FACTORS AFFECTING OUTCOME FOLLOWING ENROLMENT INTO THE THAILAND ANTIRETROVIRAL THERAPY PROGRAMME

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by

Thammasorn Piriyasupong

October 2008

ABSTRACT

Background: No evaluation has been undertaken to assess benefits of the national antiretroviral therapy program and the distribution of the benefits to various Thai social classes resulting from the roll out the programme in 2001. This study aims to test the hypothesis that there was no association between socioeconomic status of the HIV-infected patients and their HIV-related mortality. The objectives of this study include identification of benefit of the treatment in relation to survival, health-related quality of life, immunological improvement and duration on the first-line regimen as well as the exploration of factors that might influence those outcomes.

Methods: A survival study was undertaken in May 2007 analysing 501 patients who had been treated in the government ART program between May 2001 and May 2006 to identify the treatment outcomes. Secondly, a detailed evaluation was undertaken of changes of health-related quality of life in 97 participants between 2004 and 2007. The clinical analysis was undertaken in three hospitals located in Chiang Mai, Northern Thailand. The variations with regard to treatment outcomes among social classes were analysed using Kaplan-Meier and log rank test and Cox proportional hazard regression.

Results: About 16% of the patients died, their health-related quality of life tended to be stable over the period of three years. Approximately 54% and 24% of the participants could have the CD4 cell count achieved level of 200 and 500 cell/uL respectively, and 31% had to change the prescribed regimen. Low socioeconomic, not being a member of PLHA self-help group and being treated in nurse-led clinic appeared to impose a significant effect on higher mortality.

Conclusion: To expand the benefits of the programme, the government must look after closely after the underserved people with adjusting the care delivery method

Total word count 66,169 words

INDEX

TABLES

FIGURES

ACKNOWLEDGEMENTS

It has been quite a long time since I started my Ph.D. in August 2002. There are so many good and bad things that come across my life. I have faded out many times as it is not easy to always keep staying on the right tracks. Sometimes you might trip and fall on something even if you move vigilantly. However, no matter it is good or bad; I have been to this point with many supports, assistances, encouragement and helps which I have received continuously over the past six years. I would like to thank

- Luang Phu Boonpheng Kappako; to me, he is more than my parents. At the age of 81, he still teaches and encourages us to do merits. More than anything, he edifies me to practice meditation which allows me to learn the meaning of life.
- My supervisors, Dr. Alan Haycox and Dr. David Lalloo who always see some good things in me. Many thanks to their encouragement and every suggestion and guidance that made me come up again with this thesis.
- My parents and my family; I am very grateful for them. They have been with me since the start. They always support and back me up with everything. However, my father passed away two years ago, I am glad that at least I had a chance to be with him before he died.
- Prof. Harold Townson; without him, I would not have a second chance to come back again
- Asso. Prof. Ratana Panpanich, Faculty of Medicine, Chiang Mai University; to me, she looked after me as if she was my second supervisor in Thailand.
- Staff at San Sai Hospital, San Patong Hospital, Nakorn Ping Hospital, Chiang Mai; without them, I would have no data and this thesis would never be produced.
- Dr. Vittay Jarupunpol and Dr. Veerapan Supanchaiyamart, the two Directors of Khon Kaen Hospital. Dr. Sirijit Vasananan and staff at Khon Kaen Hospital whom I

work with. They are more than colleague, we have trusts in each other and we have some common beliefs that we will deliver what is goods for Thai people

- Friends in Liverpool; to have you as friends, my life could not be happier
- Mr. Thanapat, Mr. Narongrith, Mr. Sooksan, Mr. Kritpong and the group of scholars under the patronage of Luang Phu Boonpheng Kappako
- Every kindness and courtesy from many people that I might not be able to write down here, and I would not put them behind.

Thammasorn Piriyasupong

October, 2008

LIST OF ABBREVIATIONS

3TC	Lamivudine
ADAP	Medicaid and AIDS Drug Assistance Programme
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
ART	Antiretroviral therapy/treatment
ARV	Antiretroviral
ATC	Access to care
AZT	Zidovudine
BMS	Bristol Myers-Squibb
CD4	Immune cell that is the target for HIV (also called T-cell)
CMV	Cytomegalovirus
CRN	Clinical research network
CSMBS	Civil servant medical benefit scheme
d4T	Stavudine
ddI	Didanosine
DOTS	Directly observed treatment short course
EFV	Efavirenz
ER	Emergency room
GDP	Gross domestic product
GFATM	Global fund to fight AIDS, Tuberculosis, and Malaria
GPO	Government Pharmaceutical Organisation
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HR-QOL	Health-related quality of life
IDV	Indinavir

IQR	Inter-quartile range
IPD	In-patient department
IVDU, IDU	Intravenous drug user/injecting drug user/illicit drug users
LPV	Lopinavir
JICA	Japan International cooperation agency
LPV/r	Lopinavir/ritonavir
LR	Labour room
MAC	Mycobacterium avium complex
MDR-TB	Multi-drug resistance TB
MeSH	Medical Subject Heading
MOPH	Ministry of public health
MSF	Medecins Sans Frontieres
MSM	Men who have sex with men
NAPHA	National access to antiretroviral program for people living with HIV/AIDS
NESDB	National economic and social development board
NGO	Non government organisation
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
OECD	Organisation for economic co-operation and development
OI	Opportunistic infection
OPO	Out-patient department
OR	Operation room
PCP	Pneumocystis carinii pneumonia
PHA/PLHA	People who living with HIV/AIDS
PI	Protease inhibitors

PMTCT	Prevention of mother to child transmission
RTV	Ritonavir
SD	Standard deviation
SQV	Saquinavir
SQV/r	Saquinavir/ritonavir
SSS	Social security scheme
STI	Sexual transmitted disease
TB	Tuberculosis
THB	Thai Baht (currency)
TNP+	Thai Networks for people living with HV/AIDS
TNCA	Access Foundation, Thai NGO's coalition on AIDS
TRIPS	Trade-related aspects of intellectual property rights
UCS	Universal coverage scheme
TUC	Thailand MOPH-U.S. CDC collaboration (TUC)
UNAIDS	Joint United Nations programme on HIV/AIDS
$US	United States Dollar (currency)
WHO	World health organisation
WTO	World trade organisation

CHAPTER 1
INTRODUCTION

1 Introduction

HIV/AIDS is a global health problem which threatens human welfare, economics, productivity and the unity of people in society. It is a leading cause of death and is considered as a threat to national security in many countries. Fortunately, effective antiretroviral therapy (ART) is available to control the progression of disease, although only some people gain access and receive benefit from this treatment. Thus, great efforts have been made towards expanding the provision of ART to alleviate discrepancies in access especially in developing countries where the burden of the disease is highest[♣]. This chapter provides an overview of the global situation with regard to HIV/AIDS and its associated burden. Moreover, the expanded use of ART in resource-limited settings and disparity of access and benefits to the ART are outlined. At the end of this chapter, the research hypothesis and objectives are presented.

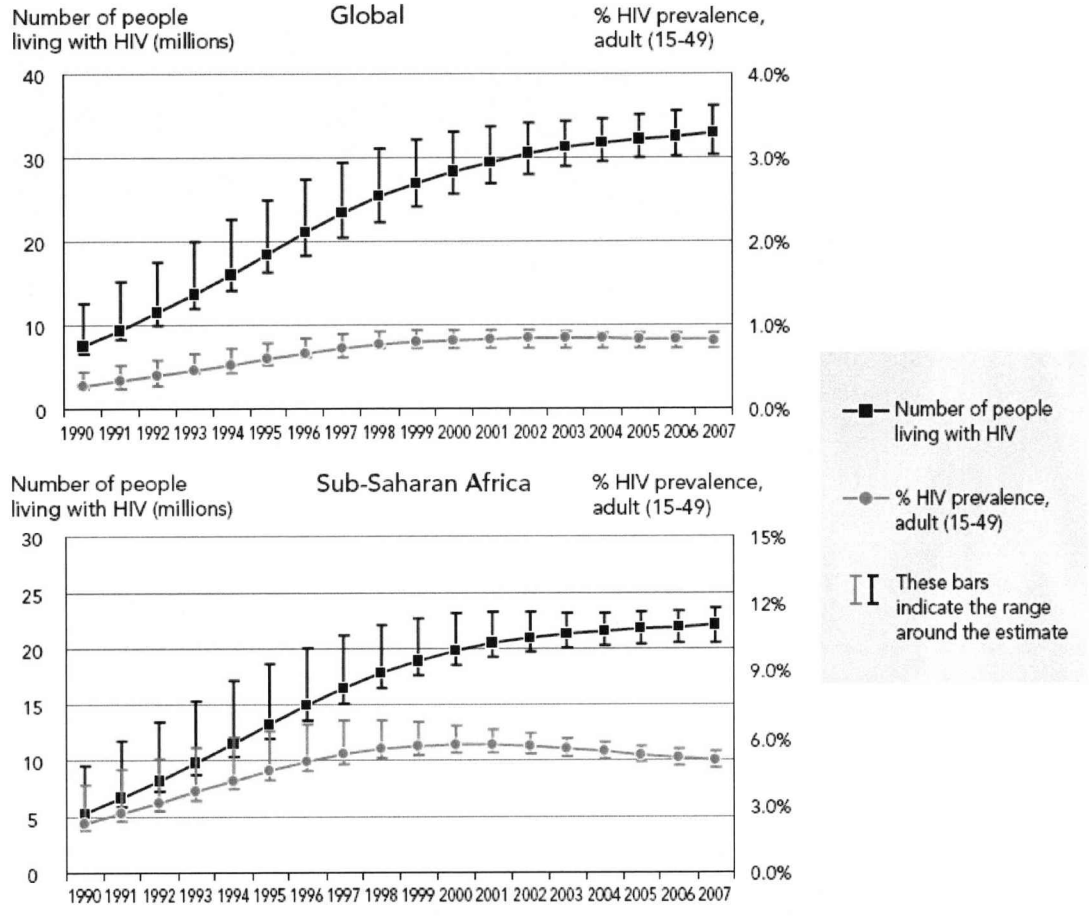
1.1 HIV/AIDS epidemic and its burden

The HIV/AIDS epidemic is imposing destructive effects in every part of the world; reaching into every level of society, impacting on young and old, rich and poor (UNAIDS 2008). The disease is dynamic and changing as the virus has developed an ability to mutate into many different variants as its environment changes (UNAIDS 2008). The annual number of HIV infected people has begun to stabilize since 2000, however, it has been estimated that 33 million people worldwide were infected with HIV and two million died of AIDS globally in 2007 (UNAIDS 2008). In relation to HIV prevalence, there has been a trend to decrease in Sub-Sahara African countries (See Figure 1-1). However, Sub-Saharan Africa remains home to about 67% of PLHA worldwide with the number of people living with HIV/AIDS

[♣] Terms as developed and developing country appeared in this thesis are defined regarding the Human Development Index (HDI) which is a comparative measure of life expectancy, literacy, education, and standard of living for countries worldwide. It is a standard means of measuring well-being, especially child welfare. It is used by the United Nation (UN) to determine and indicate whether a country is a developed, developing or under developing country. See http://hdr.undp.org/hdr2006/statistics/ for lists of the countries and for more detail

(PLHA) continuing to increase as HIV treatment extends the patients' lives (UNAIDS 2008).

Figure 1-1: Number of people living with HIV and HIV prevalence during 1990-2007



Source: UNAIDS report 2008

The focus of the disease has also been shifting; increasingly affecting women and younger age groups, with 50% of PLHA worldwide now being women and 45% of newly infected people globally being individuals aged 15-24 (UNAIDS 2008). Aside from women and the young, analysis undertaken in North America found that the most affected groups were the racial and ethnic minorities (UNAIDS 2006). The situation in Western and Central Europe is similar with the highest number of new cases and highest incidence being amongst immigrants (UNAIDS 2006).

Wherever the disease is prevalent, it imposes an enormous burden on health, economics and society. For instance, in Southern African countries with high prevalence of HIV (exceeds 20%), the average life expectancy of a person has declined to less than 50 years (UNAIDS 2008). In Swaziland, Zambia and Zimbabwe, without antiretroviral therapy programmes, average life expectancy is expected to drop below 35 (UNAIDS 2004). Aside from the shortened life expectancy, the disease also reduces the income and production capacity in families with sick members whilst simultaneously increasing household expenses due to the cost of medicines and other related costs such as funeral expenses (UNAIDS 2004).

1.2 Antiretroviral therapy in resource-limited setting

The standard of HIV/AIDS care has been developed over time; from single-drug (Fischl, Richman et al. 1987); (Volberding and Graham 1994) to combination of multi-drugs (Rutherford, Sangani et al.); (Enanoria, Ng et al. 2004). New drug combinations show potential to suppress more virus and become a benchmark for HIV treatment. Up till now HAART (Highly Active Antiretroviral Therapy) which is defined as drug regimens for patients with HIV infections that aggressively suppress HIV replication, is considered as the standard care for HIV treatment due to its ability to suppress the viral replication which results in lower level of HIV in the plasma, lower mortality and lower morbidity in the HIV-infected individuals (Palella, Delaney et al. 1998); (Enanoria, Ng et al. 2004). HAART has transformed HIV disease from a fatal disease into a chronic manageable disease bringing hope to many people living with HIV/AIDS[♣].

Introducing HAART into the health system is one of the most complex health care issues being addressed in many countries (Silversides 2001). Transferring knowledge based on

[♣] Term as rich-income, middle-income and low-income country which appear in this thesis are defined according to the World Bank definition which Economies are divided according to 2005 Gross National Income (GNI) per capita. The groups are: low income, $875 or less; lower middle income, $876 - $3,465; upper middle income, $3,466 - $10,725; and high income, $10,726 or more. See http://siteresources.worldbank.org/DATASTATISTICS/Resources/CLASS.XLS for lists of the countries and more detailed.

experiences and success of treatment in developed countries is fraught with difficulties. Recently, a meta-analysis of studies analysing ART programmes in resource-limited setting has been conducted (Ivers, Kendrick et al. 2005) which demonstrated that ART programmes can achieve similar effectiveness to results observed in developed countries. In addition to this, some small scale studies using either CD4 counts or viral load to determine the efficacy of the treatment programme also obtained similar results to the developed world (Laurent, Diakhate et al. 2002); (Djomand, Roels et al. 2003); (Kumarasamy, Solomon et al. 2003). These findings emphasised the potential for transferring knowledge and success of antiretroviral treatment to settings where resources are more restricted (Moatti, Spire et al. 2004).

Aside from ARV drugs, inadequacies of health infrastructures, including health personnel and excess demands for treatment, are considered to be major obstacles to treatment in resource-poor settings (Yazdanpanah 2004); (Kovsted 2005). Resources used for implementing ART might also require an upgrading of health infra-structures. Developing mechanisms to deliver ART to underserved groups of people, while ensuring high quality of care with acceptable costs, is required, while also being sensitive to the cultural context of the country being addressed.

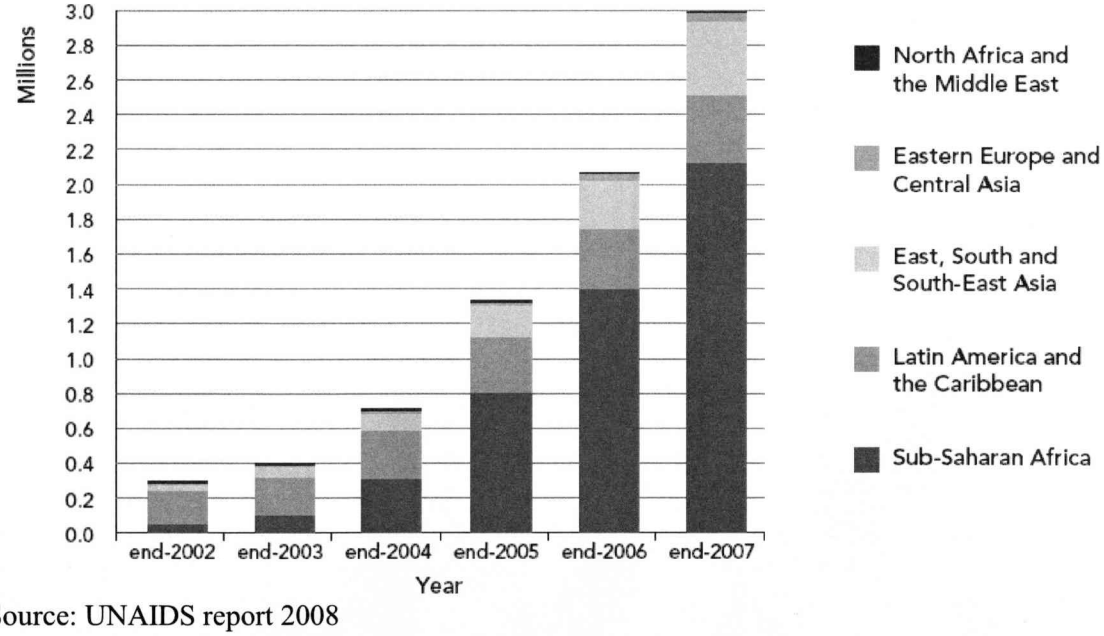
In most developed countries, HAART is provided through centres specializing in the care of HIV treatment. In contrast, in developing countries, it is unclear whether ART should be centralized providing through specialist centres, be integrated with other programmes, such as those programmes for tuberculosis, or alternatively be integrated into routine health care service (Jaffar, Govender et al. 2005); (Kovsted 2005). Service delivery through hospitals or specialist centres which are usually located in cities might lead to limited coverage, especially given the difficulty of travelling and associated expenses for patients which would be likely to intensify urban-rural inequalities in ART care accessing.

Expanding the provision of ART in low- and middle- income countries is important and requires co-operation of multi-sectors to address the problem (WHO 2002); (UNAIDS 2004). In 2003, WHO/UNAIDS launched the 3 by 5 initiative which aims to treat three million HIV-infected people in low- and middle-income countries by the end of year 2005 (Ammassari, Antinori et al. 2002); (WHO 2002); (Moatti, Spire et al. 2004). Fortunately, this target appears to be achievable (largely due to significant reductions in price and enhanced capability to produce cheap local generic antiretroviral drugs. International pharmaceutical companies have been pressurized to supply antiretroviral drugs at the lowest possible price due to the advocacy groups (Yamey 2000) and politicians such as the United Nations Global Fund (Global_Fund 2005), the US president's initiative and the Clinton Foundation (Yamey 2000).

Local production of generic antiretroviral drugs has also helped to reduce drug prices. Experience from Brazil, India and Thailand emphasized the capacity of developing countries to produce drugs to serve local requirements by transferring production to developing countries. The domestic production of generic drugs was facilitated by the Doha Declaration on the TRIPS (Trade-related aspects of intellectual property rights) Agreement and Public Health in 2001 which reiterated the right of Member States to take measures to protect public health and to address devastating public health crises such as HIV and tuberculosis (Conference 2001). In spite of reduced drug prices in many areas, the price of antiretroviral drugs remained relatively high in some countries such as Russia, Serbia and other Central and Eastern European countries (WHO and UNAIDS).

Through enhanced accessibility, it has been estimated that as many as 3 million PLHA (31%) in middle- and low-income countries will have access to antiretroviral (ARV) drugs in 2008, representing a ten fold increase over the period of six years (UNAIDS 2008). By improving access to ART, AIDS-related mortality is levelling off. However, the number of newly infected patients is also increasing every year leading to a ratio of new patients to patients with access to the ARV of 2.5:1 (UNAIDS 2008). Such under-treatment represents a threat to the global ART programme unless the overall prevalence is diminished through a comprehensive prevention programme. The ART programme should form part of a comprehensive HIV/AIDS care, however, it has been reported that only 32% of PLHA with tuberculosis received both ART and anti-tuberculosis treatment (UNAIDS 2008).

Figure 1-2: People receiving ARV drug in low-and middle-income countries



Source: UNAIDS report 2008

1.3 Disparity of access and benefit from HAART

One of the major concerns in relation to HAART expansion is that enhanced accessibility has been slowest in vulnerable and marginalised group of people such as people in low socioeconomic class, children, ethnic minority, injecting drug users and sex workers, prisoners and refugees even in countries where ARV is free of charge (Andersen, Bozzette

et al. 2000); (Rapiti, Porta et al. 2000); (Silversides 2001). Aside from inequitable access to treatment, variations in the level of benefits experienced from treatment provision amongst groups of ART beneficiaries also required detailed analysis. This might be caused by the differences of patients characteristics in term of biological background (e.g. women and race/ethnicity (Anastos, Gange et al. 2000)) or social status (e.g. low socioeconomic status (Wood, Montaner et al. 2002)). Understanding factors that contribute to discrepancies in benefit provision will help to ensure equitable benefit when HIV- infected people are successful in obtaining access to HAART.

1.4 Aims and objectives of this research

There is political pressure to provide ART in developing countries in order to expand the number of treated individuals in a short period of time. Furthermore, the treatment is life-long and expensive which makes implementation and expansion of ART in resource-limited settings more difficult especially to previously underserved groups. Given the context in which ART is provided in Thailand, it was estimated that 61% of HIV/AIDS patients are currently receiving through the national government antiretroviral therapy programme which provides care free of charge (Kanshana and Simonds 2002); (UNAIDS 2008). However, there is growing evidence of both lower levels of access and reduced benefit being experienced by vulnerable and marginalised groups of people such as people in low socioeconomic class, women and ethnic minorities or in groups of injecting drug users. This study aims to explore why ART outcomes appear to be poorer amongst such disadvantaged groups and isolate factors that might contribute to those limited outcomes.

My research question is therefore:-

"What factors affect antiretroviral therapy outcomes following enrolment into the Thai national ART programme?"

As this study focuses on the contribution of the socioeconomic status for the treatment outcome, thus, my null hypothesis is:-

"There was no association between socioeconomic status of the HIV-infected patients and their HIV-related mortality following enrolment into the Thai national ART programme"

And the objectives of this study are:-

1. To explore the characteristics of PLHA who received antiretroviral therapy in relation to baseline characteristics and their clinical information and the experiences of care provided by different types of ARV clinic (doctor- and nurse-led clinic)
2. To determine the impact of ART on treatment outcomes in relation to survival, health-related quality of life, immunologic response (CD4 cell counts) and duration on the first line regimen of the ART
3. To explore factors such as age, gender, socioeconomic, education, health insurance, being member of PLHA self-help group, native to the ART, baseline CD4 cell count, prescribed regimen and type of ARV clinic that may contribute to the treatment outcomes,

For the next chapter, inclusive literatures related to the hypothesis and objectives of the present study were reviewed and presented according to the main outcomes of the national antiretroviral therapy which were investigated in this study.

CHAPTER 2
LITERATURE REVIEW

2 Literature Review

The following chapter provides a comprehensive literature review analyzing literature relevant to the engaging of HAART in developing countries. The literature review was categorized into four main subjects: (i) outcomes of the antiretroviral therapy, (ii) factors influenced the treatment outcomes and (iii) delivery of ART in resource limited settings, and (iv) the development of national antiretroviral therapy programme in the Thai universal health settings. At the end of this chapter, a broad conclusion of the main lessons identified in the literature review is presented.

2.1 Methodology

2.1.1 Database searches

Electronic and non-electronic searching was undertaken between September 2005 and Jan 2007. Re-searching was performed during September-October 2008. The main databases searched were Medline (1966-present) and the Cochrane Central Register of Controlled Trials (Clinical Trials; CENTRAL). Hand searching was also conducted for the following Journals: AIDS (1987-2008); Journal of acquired immune deficiency syndromes (1996-2008); AIDS care (1989-2008) and; HIV clinical trials (2000-2008)

2.1.2 Search terms

For Medline and the Cochrane Library searching, keywords were used according to MeSH term (Medical Subject Heading) which is the U.S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/PubMed as these terminologies provide a consistent way to retrieve information that may use different terminology for the same concepts. The MesH terms were used either singly or in various combinations (see Table 2-1)

Table 2-1: Searching results via Medline using MeSH terms

Search using MeSH term via Medline*	As major topic; number of article found	As keywords; number of article found
Survival study regarding ART		
Survival; OR		
Mortality; OR		
Survival rate; OR		
Survival analysis;		
AND HAART	18	680
AND HAART; AND Developing countries	0	16
Health-related quality of life		
Quality of life		
AND HAART	58	192
AND HAART; AND Developing countries	0	1
Treatment outcomes of ART		
Treatment outcomes		
AND HAART	14	1564
AND HAART; AND Developing countries	0	43
Factors associated with HAART		
Socioeconomic factors; OR		
Health service needs and demand; OR		
Social class; OR		
Population characteristics		
AND HAART	288	1608
AND HAART; AND treatment outcome	0	259
AND HAART; AND Developing countries	7	79
AND HAART; AND Developing countries; AND treatment outcome	0	10
ART delivery		
National health programs; OR		
Delivery of health care; OR		
Health policy; OR		
Delivery of health care, integrated; OR		
Health services accessibility;		
AND HAART	576	1418
AND HAART; AND Developing countries	19	96

* As on September 9, 2008; MeSH=Medical subject heading

2.1.3 Selection process

Titles and abstracts (where available) were scanned; potentially relevant abstracts in English were retrieved or downloaded for obtaining full text articles. References or bibliographies of retrieved articles were scanned for further relevant articles. References were stored and managed using Endnote Programme (version 10; Thomson ResearchSoft)

2.2 ART treatment outcomes

2.2.1 Survival

As HIV/AIDS is a fatal disease, the successes of the treatment are then usually measured through the survival or mortality of the patients. The pattern of mortality has been changed since the introduction of HAART in 1996. As described in a French retrospective study which showed that the causes of death were no longer AIDS-related (Bonnet, Morlat et al. 2002). This suggests the requirement for changing of clinical monitoring of HIV/AIDS patients. The findings agreed with that found in a study from the USA which showed that the mortality rate of HIV/AIDS-related death also decreased while the rate of non HIV/AIDS-related death was quite stable (Louie, Hsu et al. 2002) or even increased (Lau, Gange et al. 2007). A Swiss study also showed the positive impact of HAART. In this study, the hospital mortality and length of stay for HIV-related admission of HIV-infected patients were declined. The annual number of admission of HIV/AIDS also decreased. However, the number of intensive care unit admission of HIV/AIDS patients increased (Nuesch, Geigy et al. 2002). Still, the mortality in HIV-infected patients even in those with a good initial response to HAART is still higher than in the general population (van Sighem, Danner et al. 2005) as HIV infection continues to contribute to the premature deaths among adults, mainly because of the late presentation (Kumar, Kilaru et al. 2006).

The positive effect of HAART has also been demonstrated in children. HAART was found to be associated with a marked decline in the progression to AIDS, improved survival in HIV-1-infected children, reduced incidence of infections and hospitalizations and decreased incidence of some organ-specific complications of HIV (Sanchez, Ramos Amador et al. 2003). In developing country such as Puerto Rico, the epidemic of HIV/AIDS mortality has also been changed since the implementation of HAART. HIV/AIDS death was significantly reduced (Mayor, Gomez et al. 2005). In Brazil which was the first developing country to provide fee and universal access to ART, between 1999 and 2004 conditions usually

considered not to be related to HIV-infection appeared to become more likely causes of death over time than reported causes of death among individuals who had HIV/AIDS listed on the death certificate than in those who did not (Pacheco, Tuboi et al. 2008). This observation has important programmatic implications for developing countries that are scaling-up access to antiretroviral therapy

2.2.2 Health- related quality of life

HIV infection is generally associated with low quality of life (Miners, Sabin et al. 2001) and has been the subject of evaluation since zidovudine was used in HIV-infected patients (Wu, Mathews et al. 1990). Such analyses provide the patients' perspective such as in the case of zidovudine, where single therapy was found to decrease quality of life (Wu, Rubin et al. 1993); (Lenderking, Gelber et al. 1994). Before the availability of HAART, mortality seemed to be the dominant outcome (Mellors, Munoz et al. 1997); (Wu 2000). However, now quality of life has become a primary goal of treatment as patients live longer and the therapy might cause various adverse effects (Wu 2000); (Henry 2000). The regimen should be chosen regarding tolerability of the patients as well as its effectiveness

In health research when we use the term "quality of life", it usually refers to health-related quality of life (HR-QOL) which includes several dimensions such as mental and physical perceptions of their health (Wu 2000). Quality of life data have added useful information to treatment trials which sometimes supports the findings of the trials (Bozzette, Kanouse et al. 1995); (Revicki, Moyle et al. 1999); (Nieuwkerk, Gisolf et al. 2000), and sometimes contradicts trial outcomes (Safrin, Finkelstein et al. 1996) emphasising the importance of obtaining information of adverse effects and tolerability rather than just survival (Nieuwkerk, Gisolf et al. 2001) or adherence (Protopopescu, Marcellin et al. 2007)

Evaluation of HR-QOL through standardized questionnaire is usually less invasive and less time consuming compared to laboratory testing. Data collection requires adequate training of interviewers or/and investigators to reduce the potential biases that might occur during the evaluation. When assessing people with poor literacy and education, data collection procedures should be tailored to get adequate and accurate information with missing data being reduced as far as possible (Wu 2000). Many standardized questionnaires have been proposed to measure HR-QOL, however, no gold standard has yet been established. Questionnaires can be divided into two broad categories (i) general measure such as EQ-5D (Jelsma, Maclean et al. 2005); (Brown, Thorne et al. 2006); (Louwagie, Bachmann et al. 2007), McGill Quality of life Questionnaire (Cohen, Hassan et al. 1996), Short form (SF) 12 (Burman, Grund et al. 2008), SF 36 (Carrieri, Spire et al. 2003); (Burgoyne and Renwick 2004); (Preau, Leport et al. 2004); (Liu, Ostrow et al. 2006); (Protopopescu, Marcellin et al. 2007), World Health Organisation Quality of Life questionnaire (WHOQOL-BREF) (Yen, Tsai et al. 2004); (Byrne and Honig 2005), NeuroQOL questionnaire (Parsons, Braaten et al. 2006) and (ii) disease specific measure such as MOS-HIV (Nieuwkerk, Gisolf et al. 2001); (Guaraldi, Murri et al. 2008) for HIV-infected patients. Recently, an Italian research group has developed the new set of self-administered questionnaire which is called *Istituto Superiore di Sanita-Quality of life* (ISSQoL) as an instrument to evaluate quality of life (Bucciardini, Murri et al. 2006). In children, different questionnaires are used such as Child Health Questionnaire parent short form (CHQ-28) (Byrne and Honig 2006). Using disease specific questionnaires does not guarantee better information as one study comparing the qualitative approach against the MOS-HIV found that the questionnaire missed or under-emphasized certain dimensions of HR-QOL in PLHA (Park-Wyllie, Strike et al. 2007).

A range of studies have shown that improved biological markers such as HIV viral load and CD4 cell counts lead to improved health related quality of life (Gill, Griffith et al. 2002); (Jia, Uphold et al. 2007), which in turn leads to good adherence to the medication

(Mannheimer, Matts et al. 2005). Regarding HAART itself, quality of life has been found to be poorer in patients who have switched regimen more than once (Protopopescu, Marcellin et al. 2007). In relation to patients perception, the baseline support and depressive symptoms have been found to be associated with positive and negative changes in physical function after 12 months of treatment (Jia, Uphold et al. 2005) and that active social support might help patients' mental health (Miners, Sabin et al. 2001); (Liu, Johnson et al. 2006); (Jia, Uphold et al. 2007).

Quality of life tends to be more sensitive to symptom changes rather than immunological or virological changes (Burgoyne, Rourke et al. 2004). Some adverse effect such as lipodystrophy which can be caused by either PI-contained or NNRTI-contained HAART regimen and can be perceived visually by patients, were found to be strongly associated with HR-QOL. Individuals with more severe lipodystrophy has worse quality of life (Guaraldi, Murri et al. 2008). In terms of psychomotor, it was found that the success or failure of HAART defined using both immunological (CD4 cell counts) and virological (HIV viral load) measurement was strongly associated with psychomotor; PLHA with slower psychomotor processing were more likely to fail (Parsons, Braaten et al. 2006).

The course of treatment is also significantly related to HR-QOL with quality of life being unchanged after the induction phase (Burgoyne and Renwick 2004); (Jelsma, Maclean et al. 2005); (Protopopescu, Marcellin et al. 2007). In one study, HR-QOL was found to be stable two years after the initiation of HAART (Burgoyne, Rourke et al. 2004). This can be explained by the fact that HAART can restore the patients' health and most of the changes occur during the initiation period. As disease progresses, their health might decline despite using HAART. This was confirmed by one small study of 68 participants over ten years (1994-2004), where participants' physical health tended to deteriorate over time while mental health was improved by using HAART (Liu, Ostrow et al. 2006).

Studies regarding quality of life in PLHA being treated with HAART are still limited in developing countries. However, some studies from those countries have shown the positive effect of HAART on quality of life. A study in South Africa suggested that using HAART was associated with higher level of HR-QOL (Louwagie, Bachmann et al. 2007) and similar findings arose in Senegal (Poupard, Ngom Gueye et al. 2007) and Uganda (Stangl, Wamai et al. 2007). These studies, nevertheless were conducted in the induction phase thus, longer follow up is required to assess the effects of HAART on HR-QOL in the long term.

2.2.3 Improvement of CD4 cell count

The CD4 count assesses the level of immune response while HIV is affecting the patients' bodies. It is used to understand how strong the immune system is (Yarchoan, Venzon et al. 1991); (Butler, Husson et al. 1992); (Allardice, McMenamin et al. 1998); (Chene, Binquet et al. 1998). In contrast, the viral load test measures the amount of HIV virus circulating in the patient blood. Regular monitoring of the CD4 count and viral load provides a good indication of the effects of HIV on patients' bodies (Hughes, Johnson et al. 1997); (O'Brien, Hartigan et al. 1997); (Hill, DeMasi et al. 1998). Test results can be used to interpret in the context of the course of HIV disease progression. Results of patients' CD4 count can help to make decisions about time to initiate HIV treatments (Kaplan, Hanson et al. 2003); (Wood, Hogg et al. 2004) or therapy to help prevent developing opportunistic infections (Hengel, Allende et al. 2002).

In term of the immunological response in relation to CD4 count, after the advent of HAART, many studies have demonstrated continuously the benefit of HAART in restoration of immune system (DeHovitz, Kovacs et al. 2000) The benefits also included preventing of opportunistic infection and HIV/AIDS related carcinoma (Jacobson, Li et al. 2002). Thus, it is imperative for monitoring of CD4 cell count continuously. Furthermore,

regarding the 3 by 5 initiative by WHO/UNAIDS, the level of CD4 count is one of the two recommended indicators (CD4 count and body weight gain) to monitoring the impact of national ART programme in rapid scaling up of the 3 by 5 initiative (WHO 2004); (WHO 2004) as it is comparatively inexpensive comparing to plasma viral load.

2.2.4 Changing of prescribing regimen

There are two main reasons for the patients to change their prescribed regimens; either developing drug resistance or adverse events. In resource-limited setting, clinical and immunological assessment (CD4 cell counts) are primarily used for initiation of the treatment, therapeutic monitoring and switching of ART regimens as the viral load is not always available (UNAIDS 2008). Antiretroviral treatment failure is, however, required to be measured by the viral load and genotyping for accurate detection. It is imperative that developing countries are equipped with these laboratory tests as drug resistance is unavoidable during the course of treatment. In one large survey in the USA three years after the widely use of HAART, it was estimated that 76% of patients had developed resistance to at least one ARV drug (Richman, Morton et al. 2004). However, as clinical management has been improved over time, the occurrence of drug resistance tends to be reduced (Phillips, Gazzard et al. 2007). A UK study found that 11% of patients would die in five years according to broad failure of three classes of ARV drugs (Phillips, Gazzard et al. 2007). Drug resistance might be even more problematic in developed countries and to lower the rate of drug resistance, HIV care should enhance adherence as there is an inverse relationship between adherence and drug resistance; the higher the rate of drug adherence, the lower the level of drug resistance (Moatti, Spire et al. 2004); (Lucas 2005).

Adverse effects are not uncommon for HIV-infected people taking HAART, with about half of patients experiencing adverse effects (UNAIDS 2008). ARV drugs have both short term and long term side effects. Types of toxicity are varied according to drug class, from

individual to individual, and could vary in severity from minor skin rashes to pancreatitis (Montessori, Press et al. 2004). As the number of drugs increase as the disease progresses, the risk of developing adverse drug reaction increases (Sollitto, Mehlman et al. 2001) potentially causing patient non-adherence to the medication or to discontinuation of treatment altogether. Management of adverse events is an essential part of ARV administration, and very challenging as, in developing countries, drug substitution may not be as feasible, making management even more complicated (UNAIDS 2008).

2.3 Factors influencing access and treatment outcomes

2.3.1 Gender

The association between gender and the utilization of HAART has gained prominence since the invention of HAART even in the developed countries. For instance, in one large interview based study the inadequate access to antiretroviral therapy was found among African Americans and women after the CD4 cell counts adjustment (Shapiro, Morton et al. 1999). This was consistent with one study published earlier which demonstrated that women were at risk of delay to get the HIV/AIDS care after the HIV diagnosis compared to men especially in group of women who learned their HIV status during their pregnancy (Ickovics, Forsyth et al. 1996). Similar findings were found in one large cohort of 9,530 patients, being female and being alcoholic decreased the likelihood to be prescribed with HAART (McNaghten, Hanson et al. 2003).

These findings also go in the same direction with results from studies assessing the use of HIV/AIDS care at various types of facilities which suggests poorer accessibility to HAART of women (Anderson and Mitchell 2000). Moreover, this was that found to be associated with perception of the patients which in one Australian study has revealed that men expressed more favourable attitudes towards HAART than women (McDonald, Bartos et al. 2001)

Gender and the use of HAART in resource-limited settings were recently explored. In Malawi, the national antiretroviral therapy programme has initiated in the fourth quarter of 2004. At the beginning, it was concerned that men rather women would be the majority who benefit from the programme (Makombe, Libamba et al. 2006). However, the programme has progressed, the disparity between men and women were still low (with the ratio of male to female=6:4). However, children were still not the target for the treatment programme. in one multi-centre study in 13 countries, the number of women who were prescribed with HAART were higher compared to men (Beusterien, Davis et al. 2008). This was later confirmed by UNAIDS report in 2008 which shows that the coverage of HAART in women is higher or at least equal to men in most of the countries (UNAIDS 2008). This might be due to that at the initial stage, women were perceived as risk group for poor access to HAART from what have found in previous studies which brought in everyone' concern during the scaling up period. But at the moment after worldwide scale up of ART, the evidence came up again that women were better than or equal to men in term of accessing HAART.

From the studies above, we found that ethnicity and gender are factors that can determine the pattern of HIV/AIDS cares utilization. Aside from the affect of ethnicity/gender on access, they also have an effect on treatment outcomes as they are ones of the baseline biological determinants of HIV/AIDS. Ethnicity and gender were also found to be related to biological difference as shown in one study which suggested that the different in the values of HIV-1 RNA and the rate of HIV-1 disease progression might be due to the influence of differences in gender and ethnicity (Anastos, Gange et al. 2000).

2.3.2 Low socioeconomic status

The relationship between socioeconomic status and the outcome of HIV/AIDS care has been analysed since it was found to be an independent predictor of HIV disease progression before the advent of HAART (Schechter, Hogg et al. 1994); (Chaisson, Keruly et al. 1995). Socioeconomic status was found to be a significant predictor of death for low income men despite adjustment for age at infection, CD4 count, use of mono or dual therapy, use of PCP prophylaxis, and years of infection were also found to be a significant predictor in disease progression. However, another study found no association between socioeconomic status and progression to AIDS and AIDS-related mortality (Wood, Montaner et al. 2002). Such different findings might be due to different care pathways with differences in HIV disease progression being due to the poor access or use of HIV/AIDS care among people with low socioeconomic status. For instance, it was found that HIV-related mortality was strongly associated with socioeconomic status, with persons from low socioeconomic status being less likely to be prescribed triple therapy (Wood, Montaner et al. 2002). However, the difference in survival by neighbourhood income level disappeared after controlling for HAART utilization (McFarland, Chen et al. 2003).

Even in the context of universal health coverage providing HAART at no cost, one Italian study showed that differences in survival of persons with AIDS still emerged by socioeconomic status. Such results may be explained by poor access to health care and poor adherence to treatment (Rapiti, Porta et al. 2000). The findings were similar with that of two subsequent studies. A study by Wood found that people from lower socioeconomic status were less likely to be prescribed HAART and their mortalities were higher compared with patients with high socioeconomic status (Wood, Montaner et al. 2002). A second study found that despite adjusting for age and CD4 cell count at start of treatment, less than 70% of patients with low socioeconomic status but more than 85% of patients with high socioeconomic status survived beyond five years of diagnosis (McFarland, Chen et al.

2003). These findings suggest that socioeconomic status, by influencing access to HAART, significantly affects the outcomes of ART in terms of mortality and disease progression.

2.3.3 Education

High long term adherence is required for the good outcome of the ART, thus, patients' education is an important factor to make the patients adhere to the treatment as shown in one study that the patients with marginal to low literacy were 3.3 times more likely to be non-adherence to HAART (Wolf, Davis et al. 2007). Patients' satisfaction with information they received about the treatment was also one of the important factor to make patients adhere or decline the treatment (Gellaitry, Cooper et al. 2005). Thus, providing information tailored to meet the needs of individual patients and address their specific concerns, in order to support informed decision making is required in the HIV patients. Moreover, a study from the USA has shown that patients with lower educational attainment less likely to gain access to HAART (Keruly, Conviser et al. 2002). In General, patients with low education attainment were less likely to be benefit from HAART.

2.3.4 Health insurance

It was also found that antiretroviral treatment tended to be prescribed in people with private insurance (who are usually richer) rather than other types of payers (Shapiro, Morton et al. 1999); (Keruly, Conviser et al. 2002); (McKinney and Marconi 2002). A study of nearly one thousand HIV-infected patients highlighted type of medical insurance as a factor determining receiving ART (Keruly, Conviser et al. 2002). In this study, it also found that females, non-white patients, IDUs, patients with lower educational attainment and patients with high CD4 cell counts/low viral load were also less likely to gain access to HAART (Keruly, Conviser et al. 2002). A study by Bhattacharya demonstrated better performance of private insurance over public insurance in protecting against premature death (Bhattacharya, Goldman et al. 2003).

2.3.5 Accessibility

Access to antiretroviral therapy (ART) for patients in low- and middle-income countries has become an increasing global public health and political concern. There are three main factors that have contributed to the expansion of ART in developing countries (Kovsted 2005). Firstly, the high and increasing prevalence rate of HIV/AIDS in developing countries requiring more resources to contain the problem and greater problems in accessing the treatment. Secondly, the concentration by the media on HIV/AIDS which partly results from aggressive NGOs driving the confrontation with pharmaceutical companies and negotiating on drug prices for poor countries. Thirdly, HAART became perceived as a fundamental human right and a high priority within public health.

Equality of access to ART should be a concern of policy makers as there is growing evidence that access to treatment is lower in underserved groups of population such as people with lower socioeconomic status (Marmot, Smith et al. 1991), ethnic minority (Fiscella, Franks et al. 2000) and injecting drug users (Strathdee, Palepu et al. 1998). Moreover, treatment outcomes such as HIV-related mortality were found to be poorer in these groups (Marmot, Smith et al. 1991); (Hogg, Strathdee et al. 1994); (Strathdee, Palepu et al. 1998); (Fiscella, Franks et al. 2000).

2.3.6 Self-help group

The shortage of health manpower in developing countries can severely aggravate the problem of poor accessibility to HAART (Muula, Chipeta et al. 2007); (Philips, Zachariah et al. 2008). It also poses unfeasible monitoring demands, drain valuable resources from more important prevention efforts (Lange and van der Waals 2002) as one study also revealed that 85 clinical officers and physicians and 91 nurses had to provide HAART to nearly 100,000 PLHA. The requirement was far less use of human resources than would be estimated based on the literature from other countries (Muula, Chipeta et al. 2007). The group of volunteer health workers might help to alleviate the problem. This role of the group

requires cooperation with community similar to that described by Farmer in 2001 about a community based approach to ART in rural Haiti (Farmer, Leandre et al. 2001). The contribution of self help group to the outcome of ART has been demonstrated continuously. For instance, it might assist PLHA to adhere to the treatment as well as to support the members throughout the course of the treatment as showed in one study (Lyttleton, Beesey et al. 2007). However, the study was done qualitatively with no outcome measures. At present, the evidences support the benefit of self-help group to the ART still need clarification.

2.3.7 Baseline CD4 cell count

Initial CD4 cell count is one of the most important factors that play a role determining the point the start to the treatment (Kaplan, Hanson et al. 2003). In developing countries, most of the patients start the treatment at a low level of CD4 cell count (usually less than 200 cell/uL), However, the benefit in term of mortality reduction can still be observed (Bogaards, Weverling et al. 2003).

The initial CD4 cell count also implied the physical well being, role function and health perception (Gill, Griffith et al. 2002). Moreover, it is also found that the low initial CD4 cell count was highly associated with the opportunistic infection such as cytomegalovirus infection (Salmon-Ceron, Mazeron et al. 2000). It was also considered a prognostic factor for the progression of disease, CD4 cell count (less than 200 cell/uL) was a determinant of being AIDS (Jacobson, Li et al. 2002); (Hulgan, Raffanti et al. 2005), mortality (Bedell, Heath et al. 2003) and a naïve CD4 cell count at baseline influenced the immunological recovery in both adults (Michael, Kirk et al. 2002) and in children (Nikolic-Djokic, Essajee et al. 2002). From what mentioned earlier, it is challenging to evaluate the effects of the CD4 cell count at baseline on the treatment outcomes.

2.3.8 Disease staging

The staging of HIV/AIDS can be done in a various way; following the definitions of the US Centers for Disease Control and Prevention (CDC) or WHO staging (Canestri, Sow et al. 2007); (Natu and Daga 2007). In 2003, WHO had developed a guideline for antiretroviral therapy which was designed to be used in developing countries. From the investigation in 2006, it has found that the 43 countries with 3 by 5 initiatives had developed their own guideline for the ART national programme which mostly derived from the WHO's guideline. According to the guideline , the point for initiation of HAART require not only the CD4 cell count but also the clinical staging (Erhabor, Uko et al. 2006); (Canestri, Sow et al. 2007). WHO clinical staging has found to be a good predictor of those who needs HAART (Lynen, Thai et al. 2006). However, the WHO classification was not sensitive to change to see the benefit of the treatment after the initiation of the therapy (Natu and Daga 2007). In the present study, it might be useful to assess the contribution of the baseline WHO staging on the treatment outcomes.

2.3.9 Regimen of ART

The development of ART has been done continuously from single regimen to triple regimen which is the current standard treatment for HIV/AIDS. Since the introduction of zidovudine in 1987, over 2,000 combinations of ARV regimens have been recorded (Ghani, Donnelly et al. 2003) and most of the modification of the treatment in the majority of patients was usually due to minor toxicities whose incidence was similar for PI-based and NNRTI-based regimens (Collier, Conway et al. 2009)

In term of effectiveness of different regimens, it found that regimens of ART; NNRTI (Non-nucleoside Reverse Transcriptase Inhibitor) -based or PI (Protease inhibitors) -based regimen were not associated with the immunological benefit of the treatment 2000); (Waters, Stebbing et al. 2004). However, a recent study from the USA showed that first-line

2NRTIs + NNRTI was cost-effective or cost-saving when compared with PI-containing regimens for all lines of therapy.

One of the concerns for choosing HAART regimen was not only its efficacy but also the patients' quality of life. PI-based therapies often fail due to poor adherence caused by heavy pill burden, complex dosing schedules and undesirable side effects. The current trend is to switch from PI-based to PI-sparing regimens (Zhang, Hamatake et al. 2004). Despite some encouraging results from NNRTI-containing therapies, two major concerns in using the currently available NNRTIs remain: (i) low genetic barrier to the emergence of drug resistance and (ii) cross-resistance due to single mutations that often render the whole class of NNRTIs ineffective. In term of adverse event, it was found that PI-based regimen was a significant risk factor for hypercholesterolemia (Tassiopoulos, Williams et al. 2008) while stavudine-contained regimens were associated with pancreatitis (Riedel, Gebo et al. 2008) and lipodystrophy was the common side effect that can occur from both types of regimen (Monnerat, Cerutti Junior et al. 2008). From the review above, it can be seen that different regimens yield different outcomes both positive and negative, thus, it is challenging to identify the contribution of different types of ART regimens on the treatment outcomes.

2.3.10 Type of ARV clinic: doctor-led versus nurse-led clinic

The Nurse practitioners have been established in North America for several decades (Brown and Grimes 1995). This was also mainly due to the shortage of doctor workforce. Moreover, the increasing roles of nurse practitioners have also been accepted in UK (Horrocks, Anderson et al. 2002) and Australia (Offredy and Townsend 2000). In the UK, NHS policy regarding NHS walk-in centres, NHS Direct, and nurse led personal medical services schemes have been developed and based on nurses rather than physicians acting as first point of contact with the health service (Horrocks, Anderson et al. 2002). Factors related to this trend of expansion in the role of nurse practitioners are improve accessibility,

availability and potentially cost saving. One review compared outcomes of care between nurse practitioners and physician in primary care in the USA was done in 1995 (Brown and Grimes 1995). A review from the USA showed that nurse practitioner had potential to deliver cares equivalent to doctor in term of quality of care. This was corresponded with a review in the UK assessing of the quality of care in short-term which showed equivalent outcome of cares delivered by nurses and doctors.

The shortage of doctors to provide cares in decentralized setting occurs in both developed and developing countries, nurses and other trained medical personnel play an important role to provide various types of care (Cullum, Spilsbury et al. 2005); (Walsh, Steiner et al. 2005) as mentioned earlier which might be able to apply to antiretroviral therapy. However, given the complexity drugs themselves, some are specific and some are general, providing cares by nurses has both potential advantages and disadvantages

In relation to provider costs, It has been purposed that nurse practitioners have potential to save costs of delivery ART due to generally lower salary (labour costs) of nurses compared to that of doctors and nurses tend to prescribe drugs strictly to the given protocol or guideline. However, two systematic reviews showed no support convincing the possible lower costs of care delivery by nurses (Laurant, Reeves et al.); (Bazian 2005). The review by Laurant also suggests that the degree of cost saving were depended on magnitude of salary differences between doctors and nurses and saving cost might be offset by the lower productivity of nurses compared to doctors (Laurant, Reeves et al.). In relation to the user costs which related to the expense travel expense to come visiting hospital and opportunity costs such as wage lost, this depends on setting of health facilities. In decentralized setting where nurses delivered ART cares, patients are more accessible, thus, lower user costs are expected.

Concerning accessibility to the ART, the decentralized settings such as community hospitals or health centres play and important role to provide ART. However, due to the usual shortage of doctor workforce in those settings, nurses are assigned to respond to works previous done by doctors. In this case, trained nurse practitioners delivering ART might be a feasible mechanism to scale up the treatment to increase the coverage of the programme. Moreover, the reachable decentralised setting would make patients incur less expense to come visiting and shorter distance to travel. Regular attendance is, then, anticipated which will have an effect on patient compliance to the treatment.

In relation to the services, nurse practitioners usually give services under the supervision or collaboration with doctors. Thus, in this case, their tasks are rather specific to the ART cares, and they might not be able to deal much with complicated cases. However, they are potential to have more time to provide more information regarding ART to patients, longer consultation time and shorter waiting time compared to doctors. This corresponds with three systematic reviews presented earlier which might result in higher satisfaction and higher compliance to the treatment (Laurant, Reeves et al.); (Brown and Grimes 1995); (Horrocks, Anderson et al. 2002). In relation to the doctor workloads, the reviews by Laurant made a notice that doctor workload, however, might not be reduced by the presence of nurse practitioners (Laurant, Reeves et al.). Many potential advantages of the nurse practitioners delivering ART have been purposed, however, they are not evident, thus, it is important to identify the potential contribution of ART mode of delivery to the treatment outcomes which is one of the objective in this study.

2.3.11 Underserved population for ART

2.3.11.1 Ethnic minority

Ethnicity is considered to be a major factor influencing the disparity in access to HAART. In the US, mortality and opportunistic infection were elevated among African American patients due to the advanced stage of disease at which treatment is initiated and less frequent use of PCP (Pneumocystis carinii pneumonia) prophylaxis (Easterbrook, Keruly et al. 1991). In a subsequent study, it was shown that race (African Americans) was the feature most strongly negatively associated with being prescribed antiretroviral therapy and PCP prophylaxis. No significant differences were identified in respect to age, sex, mode of HIV transmission, type of insurance, income, education, or place of residence (Moore, Stanton et al. 1994). African Americans have been found to be significantly less likely to be prescribed with HAART (Ghani, Donnelly et al. 2003) with race/ethnicity being found to be significantly associated with patterns of enrolment and patterns of HAART use for two ARV programmes (Medicaid and AIDS Drug Assistance Programme) (Kahn, Zhang et al. 2002). Such bias results from the eligibility rules, especially financial status which emphasizes the role of providers as one of the main barriers to access to HAART (Kahn, Zhang et al. 2002) and implies the significant role of State policies in reducing disparities in access to HIV drugs (Morin, Sengupta et al. 2002). The relationship between ethnicity and HAART was confirmed by one systematic review (see Table 2-2), which emphasized the racial/ethnic disparities that existed regarding utilization of HAART and other related medication (Palacio, Kahn et al. 2002),

Table 2-2: Summary of systematic review identifies the association between race/ethnicity and HIV- related medication utilization

Objective	To identify the association between race/ethnicity and HIV-relation medication utilization
Systematic review summary	▪ 28 reports including 40 studies were identify ▪ 14 studies found to that people whose race/ethnicity other than white were less likely to be prescribed with HAART ▪ 4 studies found that non white were less likely to be prescribed with opportunistic infection prophylaxis
Reviewers conclusions	The racial/ethnic disparities in term of HAART and related medication utilization are existed.
Reference	Palacio H, Kahn JG, Richards TA, Morin SF. Effect of race and/or ethnicity in use of antiretroviral drugs and prophylaxis for opportunistic infection: a review of the literature. *Public Health Rep* 2002;117(3):233-51; discussion 31-2.

2.3.11.2 Illicit drug users

Injection drug use is known as a primary risk for getting HIV infection, and the people who use these substances (illicit drug user-IDU) are one of the risk groups not to access to medical treatment, in relation to HAART, this is no exception. Knowing that patients are IDUs can affect the doctor decision to initiate HAART. One review from Ireland has found that physicians are generally reluctant to prescribe HAART for these patients due to possible poor adherence, and the potential for complex drug interactions to occur (Clarke and Mulcahy 2000). This finding was similar to that found from a survey in group of ART providers in the USA, it has been shown that there are resistant from the providers to prescribe ART to PLHA with history of drug user especially from physicians (Loughlin, Metsch et al. 2004). This might be due to the findings of study explored duration of initial regimen which showed that duration on first regimen prescribed in group of IDUs was significantly shorter comparing to those non-drug users (Chen, Westfall et al. 2003). It implied frequent change of drug regimen among this group of patients. This is raising another reason for not prescribing HAART to IDUs which is fears that it may result in elevated rates of drug resistance, However, there is no current study can demonstrate higher rate of drug resistance among IDUs prescribed with HAART (Wood, Hogg et al. 2005); (Aceijas, Oppenheimer et al. 2006); (Lert and Kazatchkine 2007). This makes IDUs less

likely to access to antiretroviral treatment. One USA study has shown that nearly one third of IDUs who are eligible for HAART were never been prescribed with HAART (Celentano, Galai et al. 2001). And when HAART was prescribed, its findings has shown that disease free survival were extended in both drug users and non-drug users, however, this benefit were shorter amongst group of IDUs (Poundstone, Chaisson et al. 2001). These findings was consistent with the subsequent studies from Norway and multi-centre study in Europe which show less explicit of effectiveness of HAART in relation to progression to AIDS, life-expectancy and HIV-related mortality in IDUs compared to other group of patients (Amundsen and Fekjaer 2003); (Chen, Westfall et al. 2003); (van Asten, Boufassa et al. 2003); (Mocroft, Gatell et al. 2004); (Galai, Vlahov et al. 2005); (Lloyd-Smith, Brodkin et al. 2006).

The coverage of HAART in IDUs in developing and transitional countries is found more problematic, one review has described that among these 50 countries, 34,000 IDUs have access to the treatment and approximately 30,000 were in Brazil. The situation is worse in South-east Asia where only 1.8% of IDUs can access to the treatment (Aceijas, Oppenheimer et al. 2006). However, the poorer effective and prognosis of HAART of IDUs in Brazil was not much different found what found in previous studies (Melo, Caiaffa et al. 2006). The UNAIDS report in 2008 also mentioned that the IDU is a group at risk not to accessing HAART (UNAIDS 2008). From the findings above, they suggests the less likely for IDUs to get access to the antiretroviral treatment, but when they were prescribed, the benefit from the treatment was less clear comparing to other group of patients. This might be due to the poor acceptance and poor adherence of the treatment which was the result from chaotic lifestyle and complex social background (Zaccarelli, Barracchini et al. 2002); (Clarke, Delamere et al. 2003); (Tourret, Tostivint et al. 2007).

2.3.11.3 Children

In the report by the UNAIDS recently, it has stated poorer access to HIV/AIDS care including ART in the group HIV-infected children (UNAIDS 2008) even though there was an evidence that the effectiveness of ART in children was similar to that observed in the adults (Gortmaker, Hughes et al. 2001). And in spite of the fact that children with 50% of children with HIV will died in the first two years without any treatment (Fassinou, Elenga et al. 2004) and 89% will died before their third birthday (Taha, Graham et al. 2000), coverage of HAART in children tended to be relatively lower compared to adults (UNAIDS 2008). In the developed countries like in the USA, the number of children with HIV is now diminishing due to one important factor is that they are managed to survive by HAART and growing up becoming adults (Harwell and Obaro 2006). By far, the substantial benefit of providing antiretroviral treatment in children can be envisaged, and scaling up the ART in this population subgroup requires higher attention.

2.3.11.4 Gay men

Gay men are another group at risk of less access to HAART as this might be caused by less awareness of HAART in this group. A study in young American gay men (aged 17-22) with ethnicity diversity, it has found that they did not aware of HAART after two years since its introduction (Koblin, Perdue et al. 2003). In another study which conducted in six thousand gay men in five big cities including Paris, London, Melbourne, Sydney and Vancouver, it has shown that gay men in these cities were not much optimistic toward HAART despite the fact that these cities had provide HAART free of charge for more than four years at the time of study conducted (Optimism 2003). In one study, it has shown that nearly 15% of men who have sex with men (MSM) were using antiretroviral care less than recommended level (poor adherence), and in addition to this, their youth was found to be a barrier to ART (Stall, Pollack et al. 2001).

2.3.11.5 Sex workers

Sex workers are another disadvantage group to access to HAART as they are suffered from the attitude that they are not worthy of the treatment. They might be also reluctant to seek

for HIV testing and the initiation of antiretroviral treatment is usually delayed. This can cause the treatment less effective and the opportunistic infection may prevent the use of ART (Wood, Montaner et al. 2003). People who are in prison also have known to be likely to be delay to get HAART (Pontali 2005). Another group is people in place where political instability which creates population movement are also considered as vulnerable group of ART as continuity of the treatment (adherence) appeared to be difficult (Saracino, El-Hamad et al. 2005). Another risk group is people with low education like those mentioned in one study from the USA with convenient sample of 204 PLHA, it has shown that around one-third of PLHA had limited literacy skill. Moreover, they were tended to have a poorer understanding of essential aspects of ART which could cause problem of access and adhere to HAART (Wolf, Davis et al. 2005)

2.4 Effects of social inequality on benefit of HAART

Most of studies mentioned above aim mainly at studying the access or prognosis of patients such as progression of the disease and HIV-related mortality with HIV which were influenced by social and biological factors e.g. low socioeconomic, women, ethnicity minority and the others. However, in this vulnerable- marginalised people, other differences aside from disparity in term of access can also contribute to the differences of outcomes of ART which can confound the relationship between those factors and the treatment outcomes

2.4.1 Differences in adherence of the treatment

As HAART has turned the nature of HIV/AIDS to a chronic disease, the clinical goals of the treatment are to maximize life expectancy while enhancing quality of life and containing the adverse effects. The goals of treatment can be achieved by maintaining suppression of the viral load below the level of 50 copies/mL (Pilcher, Miller et al. 1999). At this level, it can enhance the immunological restoration as well as prevent the evolution of drug-resistance virus (Hermankova, Ray et al. 2001); (Hunt, Deeks et al. 2003). To attain long-term suppression of the virus, it requires near perfect adherence to the treatment. For poor

adherence patient, viral drug resistance can make current treatment ineffective (Hirsch, Conway et al. 1998); (Hirsch, Brun-Vezinet et al. 2000); (Hirsch, Brun-Vezinet et al. 2003). Moreover, when this drug-resistance strain virus transmits to other people it can limit the options for treatment. Concerning relationship between time on treatment and adherence, a multi-centre AIDS cohort study has shown that poor adherence tended to develop over time of the treatment, and the adherence was associated with patient characteristic and medication factor (Kleeberger, Buechner et al. 2004).

Patient-related factors are considered as the most important determinant of good adherence (Chesney 2000). This includes patient socioeconomic status, psychosocial status, life style, and substance abuse (Bouhnik, Chesney et al. 2002); (Starace, Ammassari et al. 2002); (Carrieri, Chesney et al. 2003). For instance, depression which is the one of most common mental health problem in HIV-infected patients is considered as a risk that can cause sub-optimal adherence (Starace, Ammassari et al. 2002). Low adherence is also found in group of patients with substance abuse especially injecting drug users which have been demonstrated of failure to adhere to treatment (Bouhnik, Chesney et al. 2002); (Carrieri, Chesney et al. 2003). Moreover, interaction such as provider-patient relationship, communication, drug information with respect to patient education which advise patient the benefit and caution of the treatment are found to influence the adherence as well (Weiss, French et al. 2003). It might not be the direct effect of patients' characteristics over the treatment outcomes, but with certain characteristics of the PLHA, it can cause patients difficulties to adhere and leads to poor outcomes at the end.

2.4.2 Differences in co-morbidity

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection is an important and frequent situation, largely found in injecting drug users (IDUs) (Rockstroh and Spengler 2004); (Rockstroh and Vogel 2004); (Mayor, Gomez et al. 2006). In one

study, the prevalence of HCV was 81% in IDUs, with a predominance of HCV genotype 1. Patient with co-infected patients had significantly higher liver damage as a cause of mortality when compared with those who were not co-infected (Mayor, Gomez et al. 2006); (Nakimuli-Mpungu, Musisi et al. 2006). Another co-morbidity can be found with HIV infection are psychiatric disease (Morrison, Petitto et al. 2002); (Himelhoch, Moore et al. 2004) especially in group of women. In one study, it has found that HIV-seropositive women without current substance abuse exhibited a significantly higher rate of major depressive disorder and more symptoms of depression and anxiety than did a group of HIV-sero-negative women with similar demographic characteristics (Morrison, Petitto et al. 2002). Some findings has suggested that impairment of the immunological system might be the cause of depression (Cruess, Douglas et al. 2005). And, not only depression, mania secondary to HIV infection can be observed in people living with HIV/AIDS as well (Nakimuli-Mpungu, Musisi et al. 2006). Again, this showed that co-morbidity both physical and mental was a hidden factor that influence over the outcome

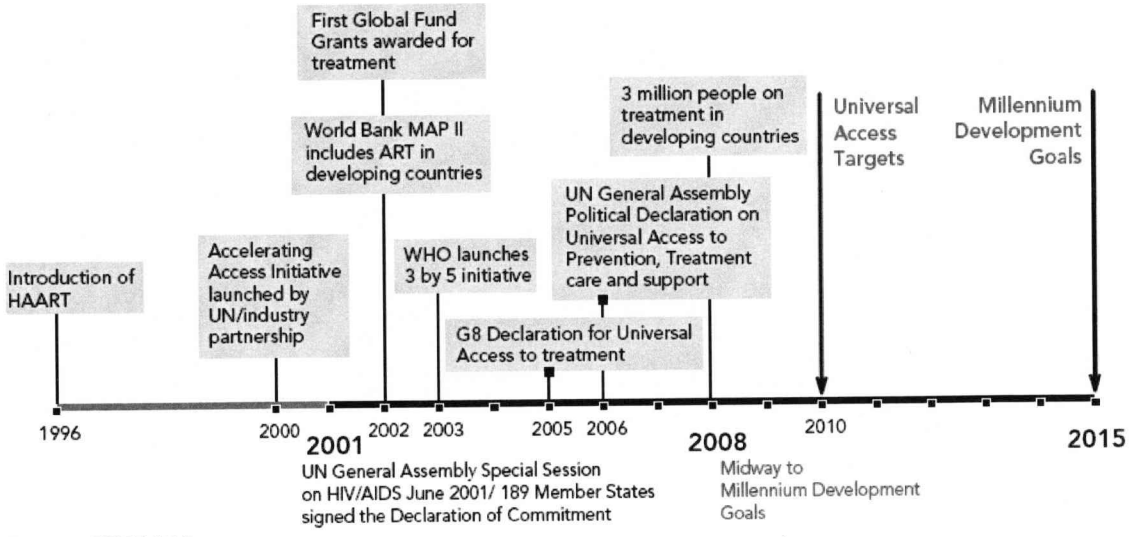
2.4.3 Differences in living conditions and health behaviour

Living conditions and life style as well as health behaviour have effects that may contribute to course and disease progression of the HIV infection. Life style factors such as injecting drug use, alcohol and substance abuse, unemployment, low socioeconomic status, homelessness, incarceration, immigration have influences over their behaviours including diet, exercise, smoking, substance abuse (Dray-Spira and Lert 2003). Moreover this could aggravate adverse effects of the antiretroviral treatment particularly lipodystrophy (Tershakovec, Frank et al. 2004). Moreover, in group of injecting drug users, potential drug interactions between methadone, and many of antiretroviral drugs has been anticipated and this contribute to non-adherence and poor clinical outcome. Therefore, optimizing ART for IDUs is necessarily required (McCance-Katz 2005).

2.5 *Delivery of antiretroviral therapy in resource-limited settings*

The treatment of HIV/AIDS has been evolved continuously (Fischl, Richman et al. 1987); (Volberding and Graham 1994) till present where combination antiretroviral is recognized as a standard of care (Rutherford, Sangani et al.); (Enanoria, Ng et al. 2004) due to its ability to suppress the viral replication. According to this, mortality and morbidity in the HIV-infected individuals are decreased (Palella, Delaney et al. 1998); (Enanoria, Ng et al. 2004). The treatment is also accepted as a cost minimizing intervention as the potential to lower total health care cost and cost-effective treatment comparing to previous single and dual therapies as the benefits from ART were found to be outweigh the high incremental cost (Sendi, Craig et al. 1999); (Anis, Guh et al. 2000); (Moore 2000); (Trueman, Youle et al. 2000); (Freedberg, Losina et al. 2001); (Schrooten, Dreezen et al. 2002); (Sendi, Gafni et al. 2002); (Krentz, Auld et al. 2003) even though the cost study at that time was based on the relatively high drug cost that was in existence at the time of the study. This leads to the conclusion that cover should be expanded to all individuals who require the treatment. Experiences of utilization of ART, however, come mostly from developed countries as presented in Table 2-1; it has been shown that relatively less literatures were from developing countries. For instance, when combining the search term "developing countries" as MeSH major topic in field of health related quality of life, survival study or treatment outcomes of ART, there was no literature found from the Medline search. The applicability of knowledge gained in developed countries to developing countries thus is not straightforward, irrespective of the quality of the evidence presented. Assessing the extent of dissemination or transferability of knowledge is therefore very challenging (Garner, Kale et al. 1998); (Murray and Frenk 2001); (Page, Heller et al. 2003); (Garner, Meremikwu et al. 2004); (Chinnock, Siegfried et al. 2005); (Moayyeri and Soltani 2005).

Figure 2-1: Events regarding scaling up of ART in low- and middle-income countries and timeline



Source: UNAIDS report

In the early stages, the cost of therapy meant that the benefits of HAART were confined to those countries in North America and Western Europe who could afford treatment. In this manner, the disparity between rich and poor countries regarding ART became increasingly noticeable over time. This led the United Nations to initiate the Joint Programme on HIV and AIDS (UNAIDS) combined with the World Health Organisation and the World Bank to identify methods to increase access to HAART (see Figure 2-1). Medical Access Programme was launched by UNAIDS in 1996 which initially benefited countries such as Uganda, Ivory Coast, Chile and Vietnam. Later Multi-country AIDS Project (MAP) developed by the World Bank allowed countries to use its funds to buy ARV drugs. Later, one of the largest efforts of ART expansion was done through the "3x5 initiatives" by WHO. Despite of the failure to reach the target of 3 million, the number of beneficiaries from HAART in Africa was increased to nearly a million in 2005 (Katabira and Oelrichs 2007).

The United States' President's Emergency Plan for AIDS Relief (PEPFAR) programme represented another major initiative to enhance access to treatment. This programme is now benefiting 15 countries most affected by the HIV epidemic and which contributes

approximately 50% of its budget for treatment and the Global Fund for AIDS, TB and Malaria. At the same time, the drug industries have lowered the prices of ARV drugs and generic versions of these medicines have been introduced (Katabira and Oelrichs 2007). However, achieving universal access to HAART in resource-limited setting still has a long way to go.

2.5.1 Exemplars of HAART programme in developing countries

Apart from doubts regarding the feasibility of implementing ART in developing countries, information regarding efficacy of ART in resource-poor settings is still scant, with the vast majority of evidence being derived from developed countries where people, resources and technologies are vastly different. Box 2-1 shows the differences of health care experiences from developed and less developed countries. In relation to HIV/AIDS patients, people from less developed world tended to present late; the level of CD4 cell count required to initiate the treatment in rich countries is usually higher than that found in developing countries. However, one study which explored the provision of HAART to patients in a resource-poor setting, found that the therapy could lead to equivalent treatment outcomes to those with high CD4 cell counts in those achieved in patients whose CD4 cell count was less than 200 cell/uL (Bogaards, Weverling et al. 2003).

Box 2-1: Comparison of the Health Care Experiences in the Less Developed and Developed Worlds

Features of the typical health care experience of a patient living in the less developed world include

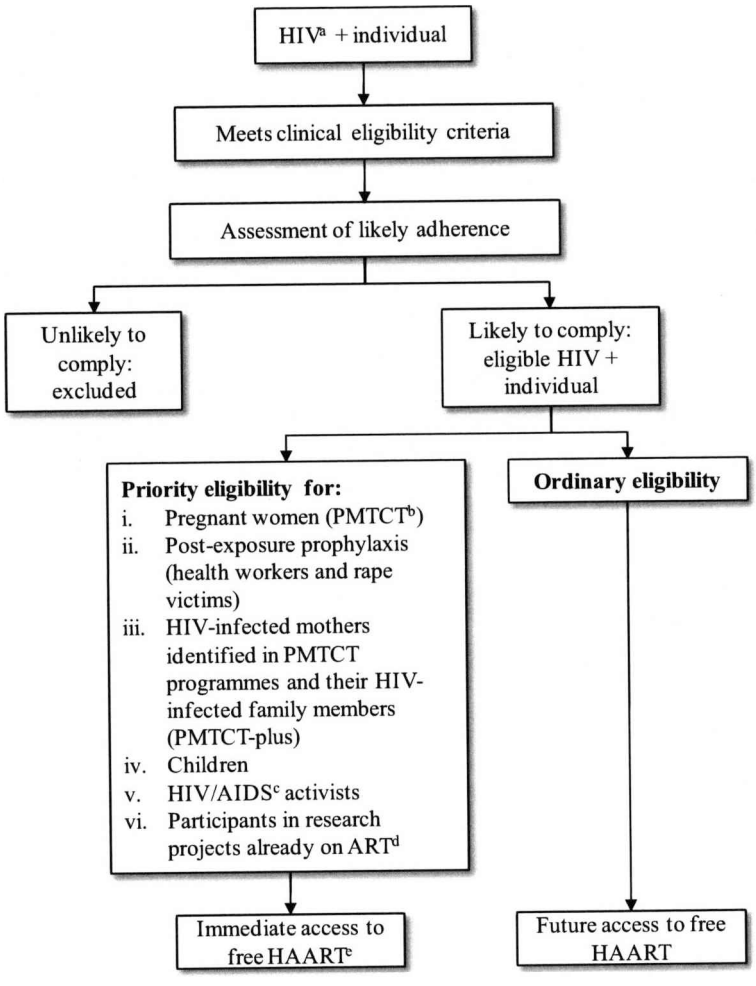
- late presentation
- self-medication of "prescription" drugs or traditional treatments
- poor facilities may delay diagnosis
- referral (if needed) not easily arranged
- if a child, may be malnourished
- if a woman, may be anaemic
- will experience problems because of shortages of trained staff
- …and because of poor infection control
- …and because of a lack of follow-up care
- patient may be unable (e.g., because of lack of funds) to fully adhere to treatment.

Features of the typical health care experience of a patient in a clinical trial in a developed country include

- none of the above

Source: Chinnock P, Siegfried N, Clarke M. Is evidence-based medicine relevant to the developing world? *PLoS Med* 2005;2(5):e107.

Figure 2-2: Selection process for ARV in Uganda



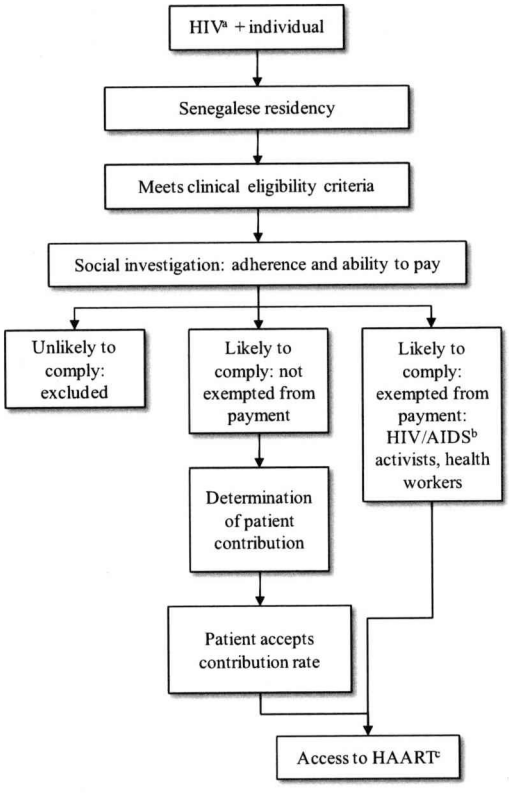
[a] Human Immunodeficiency virus
[b] Prevention of mother-to-child transmission
[c] Acquired Immunodeficiency virus
[d] Antiretroviral treatment
[e] Highly active antiretroviral therapy

Source: World Health Organisation

Demand for ARV in developing countries usually outstrips supply. To deal with this, "targeting priority recipients" have to be identified. The policy makers have to decide who can access the therapy and who has to wait until the nationwide ART programme is available (Bennett and Chanfreau 2005). Eligibility for entering the ART programme in this manner can be considered as a form of prioritization. Prioritizing is not new and is common in environments where resources are scarce such as Uganda. The ARV programme developed from the Joint Clinical Research Centre (initiated in 1992) and Drug Access Initiative (1998) (Bennett and Chanfreau 2005). In 2003, the draft policy defines criteria of

accessing to ART programme was launched. Since then, PLHA will be classified as "priority eligibility" which refers to those who can access to the drug immediately and "ordinary eligibility" which refer to PLHA who will receive the treatment later. Aside from the judgement based on clinical eligibility and likelihood to adhere to the treatment, social criteria such as being children and being activists are used for prioritization (Bennett and Chanfreau 2005) (see Figure 2-2).

Figure 2-3: Selection process of ISAARV



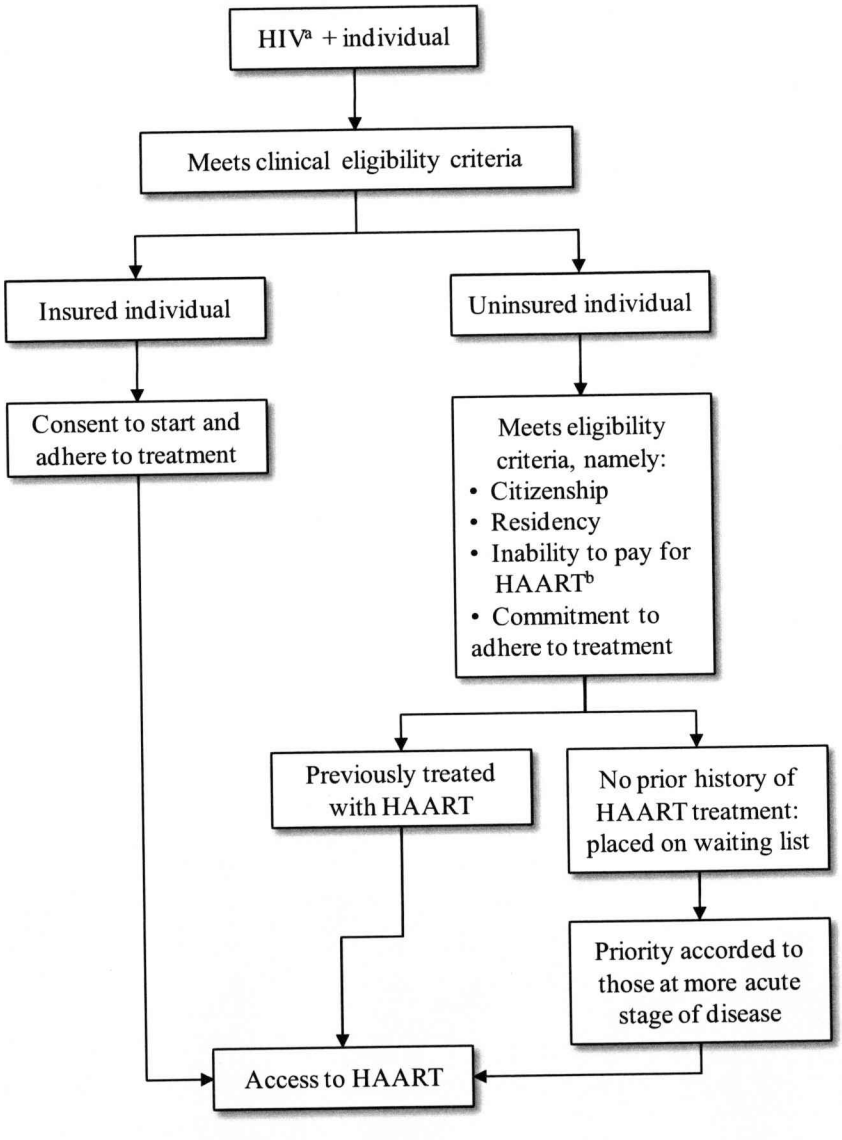
[a] Human Immunodeficiency virus
[b] Acquired Immunodeficiency virus
[c] Highly active antiretroviral therapy

Source: World Health Organisation

In Senegal, the Senegalese initiative for access to antiretroviral drugs (ISAARV) was launched in 1998-2001 to treat a total of 339 patients in limited number of hospitals under the cost sharing health scheme. It was the pilot project to demonstrate the feasibility and efficacy of ART in Africa. HIV-infected patients were included with pre-selection process and the infra-structure was set up in a research design. Patients' residency is the first

criterion for entering the programme with patients being tested for biomedical data to determine the eligibility for ARV drugs and the final stage being an assessment of their potential to adhere to ARV and to pay (Bennett and Chanfreau 2005) (see Figure 2-3). The programme planned to provide the care to cover 7,000 individuals in 2006 and the programme has been free of charge since December 2003 (Desclaux, Ciss et al. 2003).

Figure 2-4: Selection process for ARV in Mexico



[a] Human Immunodeficiency virus
[b] Highly active antiretroviral therapy

Source: World Health Organisation

In Mexico, the ART programme was launched in August 2003 with commitment from the Mexican President to provide ARV to all patients in need, with the Ministry of Health providing the drug free of charge (Bennett and Chanfreau 2005). Aside from clinical eligibility, insurance status was another important criterion (see Figure 2-4) with additional criteria being applied due to a shortfall of funding leading to interruption of drug supply. To enhance funding, the government of each state can contribute extra funding to aid the programme; however, this is still not uniform (Bennett and Chanfreau 2005).

In term of efficacy of the programme in the resource-limited settings, some pilot projects identified the successful outcomes after implementation of ART. Middle-income countries such as Brazil, with advanced ART programmes have shown to improve survival after the introduction of ART into the country (Gadelha, Accacio et al. 2002). A significant decrease of opportunistic infection incidence among HIV-infected patients after ART was also observed (Levi and Vitoria 2002). In relation to benefit in monetary term, it has been estimated that $US 1 billion had been saved since the universal access to ARV in 2001 mostly by reducing hospitalization and other HIV/AIDS care costs (Creese, Floyd et al. 2002); (Levi and Vitoria 2002); (Nunn, Fonseca et al. 2007). Brazil therefore represents one of the most successful examples of large scale ART programmes in middle-income countries, countering the belief that prevention represented the only cost-effective method to address HIV in resource-poor countries (Creese, Floyd et al. 2002).

In the case of rural Haiti, where resources are even more scarce than Brazil, ART was delivered in a small area in the country by integrating the ART programme into the existing tuberculosis-control infrastructure using directly observed therapy (DOT-HAART) as a tool to improve adherence (Farmer, Leandre et al. 2001). Clinical monitoring was undertaken using available basic laboratory facilities. The study was, however, conducted in the well controlled environment confined to 60 rural Haitians and DOT-HAART appears to be

labour intensive for such life-long treatment. However, this study has highlighted the value of increasing the cohesion between TB and HIV care as another feasible strategy to deliver HAART in resource-limited settings (Abdool-Karim, Abdool-Karim et al. 2004).

In the context of Asian countries, recently a Chinese study was conducted to test the feasibility of delivering HAART in rural China in a group of 42 PLHA. This pilot was implemented using the existing health infrastructure, only CD4 cell count was available, no viral load monitoring and quality of life measured only by the ability of the patients to return to work. The study findings have shown that these patients could be effectively supported by the programme for a period of one year (Meng, Anderson et al. 2006).

Table 2-3: Summary of meta-analysis of efficacy of antiretroviral therapy programmes in resource-poor settings

Objective	To determine the efficacy of ART programmes in the developing world and to compare the outcomes with typical outcomes in the developed countries
Systematic review summary	▪ Ten studies involving with 2,646 HIV-infected people were included ▪ Proportion of patients with undetected viral load after 12 months of treatment was 0.57 (95% CI, 0.43-0.72) ▪ Provision of free medication was associated with higher of probability of and undetectable viral load at 6 and 12 months after treatment
Reviewers conclusions	Viral suppression in developing countries was similar to that observed in developed countries after 12 months of therapy.
Reference	Ivers LC, Kendrick D, Doucette K. Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. *Clin Infect Dis* 2005;41(2):217-24.

In assessing the effectiveness of programmes serving low income countries, a recent meta-analysis of studies related to ART in resource-limited setting has been conducted (Table 2-3) (Ivers, Kendrick et al. 2005). The review demonstrated that ART was equally effective in resource-limited setting as it was in developed countries. A total of ten studies were included in this reviews which were all from Africa countries comprised South Africa, Cote

d'Ivore, Senegal, Cameroon, Uganda and Kenya and one multinational*. Moreover, most of the included studies were conducted in urban areas. Thus, validity and generalisability of success of ART in developing countries are still questioned. Aside from this, some other small scale studies in Cote d'Ivore, Southern India, China and Senegal using either CD4 counts or viral load to determine the efficacy of the treatment programme also showed the similarity of the results to those developed world (Laurent, Diakhate et al. 2002); (Djomand, Roels et al. 2003); (Kumarasamy, Solomon et al. 2003); (Meng, Anderson et al. 2006).

It is important to emphasise, however, that the success of short-term evaluation of ART in some developing countries is not a premise for the expansion of HAART to every resource-limited country due to the limited ability to generalize and the need for long-term close-up monitoring. A study from Lusaka, Zambia exhibited the downside of district-wide implementation of HAART. After the ART programme was initiated in the area, a high rate of loss to follow-up was noted. For those who were lost to follow-up, only half were traceable and half of these traceable patients had died (Krebs, Chi et al. 2008). Findings like these are to be expected especially in places where patients are very sick and are provided with care under a poor infrastructure. Wide scale expansion of the ART programme, thus, needs to be very carefully planned and monitored.

2.5.2 Monetary resources and financing system

The most important objections to the delivery of HAART in resource-poor settings are (i) the high drug cost and (ii) poor management of health infrastructures (Farmer, Leandre et al. 2001). The cost of providing HAART is still one of the biggest obstacles to accessing antiretroviral therapy (Steinbrook 2001) despite the significant reduction in drug price. Many studies undertaken in developed countries emphasise the potential resource savings from HAART. For example, Bozzette analysed three thousand Americans and found that

* Multinational study involved with 743 patients from 7 countries including Malawi, Kenya, South Africa, Cameroon, Cambodia, Thailand and Guatemala

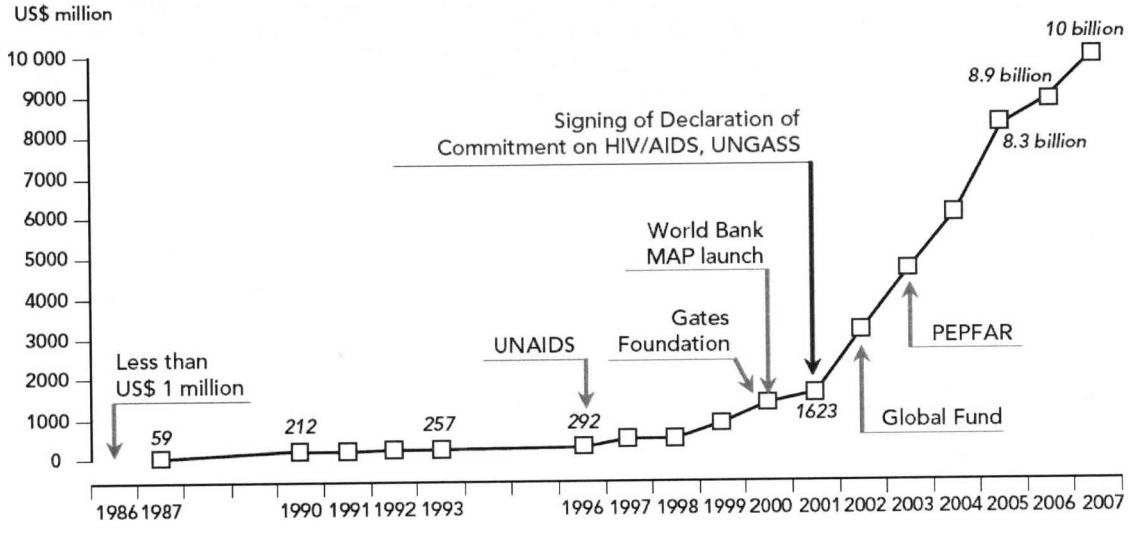
total healthcare cost declined over the study period, with overall costs reduced by 16% and hospital costs reduced by 43%, emphasizing the potential for ART to reduce lifetime healthcare costs (Bozzette, Joyce et al. 2001). Another study conducted in Medicaid-insured patients found that although the cost of drugs increased over the period analysed, the total health care cost was stable (Gebo, Chaisson et al. 1999). The same trend was observed in an Italian cohort study covering six years, which found that death had declined over the period of the study, while costs were relatively stable (Merito, Bonaccorsi et al. 2005).

Concern relating to the cost of HIV/AIDS is still prevalent with Keiser finding that costs due to drug resistance might outweigh other aspects of healthcare cost as patients would require treatment with more intensive salvage regimens which will lead to significant additional cost (Keiser, Nassar et al. 2001). To examine this, in one study, total net costs of expanding Medicaid for PLHA to improve access to HAART was modelled using a Markov model of HIV disease progression. A total of 38,000 HIV-infected patients were analysed over five years and the costs of salvage regimen (multiple-drug ART, 4-6 combination of ART regimen) were assessed (Kahn, Haile et al. 2001). Despite the fact that high cost regimens were used, the study showed the potential of ART to cut down the total care costs but emphasized that the results were sensitive to changes in drug costs and the number of patients on salvage regimens.

A recent review analysed the direct costs of providing care for PLHA from nine studies from Canada, France, Italy and the USA (Levy, James et al. 2006). Unfortunately, large discrepancies were found in the method used, population and components of costs between the studies, making direct comparisons between studies and meta-analysis of the findings difficult. No conclusion could be drawn based on the existing evidence with regard to costs as it depended on the context in which care was provided. However, it emphasizes the potential for HAART to lower the health care costs. This potential is enhanced by the fact

that drug prices have reduced significantly which would affect the findings of all HAART analyses undertaken in the past. However, evaluating total healthcare costs also needs to take into account other issues including health systems, intellectual property regulations-generic drug production, epidemiological profiles, and treatment guidelines in each setting (Nunn, Fonseca et al. 2007).

Figure 2-5: Total annual resources available for AIDS 1986-2007



Notes: [1] 1986–2000 figures are for international funds only
[2] Domestic funds are included from 2001 onwards
[i] 1996-2005 data: Extracted from 2006 Report on the Global AIDS Epidemic (UNAIDS, 2006)
[ii] 1986-1993 data: Mann.&. Tarantola, 1996

Source: UNAIDS report (UNAIDS and WHO estimation, 2007)

The cost of antiretroviral drugs represents less than 0.1% of the gross domestic product (GDP) of high-income countries (Moatti, N'Doye et al. 2003). In contrast, given the magnitude of the problem in developing countries, expenditure on ART has the potential to consume a major proportion of their health spending and account for a significant share of their GDP (Hogg, Weber et al. 1998). Figure 2-5 emphasizes the extensive mobilization of resources to resource-limited settings to support ART programme expansion. However, the issues of sustainable and self-reliance are still debatable (Steinbrook 2002).

The financial structure of the healthcare system is another important factor underpinning access to care. The utilization of healthcare is undoubtedly influenced by health financing

schemes. For instance, in the United States, HAART was more likely to be used by patients who were commercially insured than in other payer groups (Keruly, Conviser et al. 2002). To increase access to ART, the government expanded Medicaid eligibility to cover more uninsured people, however, the coverage of ART remained limited (Steinbrook 2001); (Bailey, Van Brunt et al. 2003); (Bailey, Van Brunt et al. 2004). Moreover, the financing system can affect the enrolment process, with patterns of enrolment and patterns of HAART use being linked. Such linkage results from the eligibility rules which limits access to HAART and represents a major barrier to access to HAART (Kahn, Zhang et al. 2002) but which can be used to reduce disparities in the use of HIV drugs (Morin, Sengupta et al. 2002) through altering structures of medical insurance to enhance access to ART (Keruly, Conviser et al. 2002).With sparse information of effective financing schemes and its significant effect on HAART accessibility, countries must choose the detailed service specifications to suit their own context

2.5.3 Human resources for HIV/AIDS care

In addition to drug costs, lack of adequate health infrastructure including human resources, laboratory testing, monitoring facilities, supplies and distribution management, will also constitute a major expense (Yazdanpanah 2004); (Kovsted 2005). Inequality of health resource distribution is found in developing countries with most resources being concentrated in big cities. This inequality could adversely affect the effectiveness of antiretroviral care.

Kober identified a common problem relating to the shortage of medical personnel in Malawi, Mozambique, Swaziland, and South Africa (Kober and Van Damme 2004) and found that this lack of health personnel represented the biggest obstacle to expanding ART in those countries (Kober and Van Damme 2004). Demand for health workers in African countries far exceeds their supply. For instance, in Thyolo-a small district in Malawi, only

40% of health posts in the public sector were filled while the number of patient has increased many fold since the launching of 3x5 initiatives with more than 80% of patients admitted exhibiting HIV/AIDS associated conditions (Kober and Van Damme 2004). Such staff shortages are aggravated by a drain of health personnel due to the movement of health personnel from public to private, from rural to urban and from developing countries to developed countries which intensifies the scarcity of health manpower. Moreover, the high mortality rate of HIV-infection among health personnel also enhances the scarcity of care givers (UNAIDS 2001); (USAID 2003).

It was estimated by WHO that 100,000 care trained health personnel were required to provide the care to meet the 3 by 5 goal (PEPFAR 2006) requiring enhanced cooperation between donors and governments. However, donors projects are usually restricted to the provision of resources for capital costs or for foreign exchange requirements (e.g., drug supply, training), but not for resource costs such as salary support or enhancement. Additionally, the donor projects recruit their own staff which can exacerbate the problem (USAID 2003). In a study from Malawi where the number of adults infected with HIV was as high as a million cases, it was found that the numbers of physicians and nurse were only 610 and 4,200 respectively in 2006 (Muula, Chipeta et al. 2007). To deal with this situation, the doctor had to see at least 40 patients every day, 30 days a month to reach 1,000 patients per doctor (Muula, Chipeta et al. 2007). This situation is not uncommon and can be found in many other African countries (see Table 2-4).

Table 2-4: Number of doctors and nurses in selected countries

Country	Number of (per 100,000 inhabitants)	
	Doctor	nurse
WHO minimum standard	20	100
Malawi	2	56.4
Lesotho	5	63
Mozambique	2.6	20
South Africa	74.3	393
USA	247	901
UK	222	1170

Source: World Health Organisation (WHO). Working together for health: the World Health Report 2006. Geneva, Switzerland: WHO, 2006.

Given the shortage of skilled staff, task shifting for ART delivery becomes essential. Task shifting is not a new concept in Africa, specific cadres of non-physician health personnel have been initiated to undertake clinical tasks where doctors are inadequate (Philips, Zachariah et al. 2008). Task shifting has been opted for in many African countries such as Ethiopia, Malawi and Uganda as a model by which to deliver HAART. However, this might not be an answer in case of HIV/AIDS care. In the district of Thyolo, Malawi, 450 new patients were initiated on ART every day during the early expansion phase of ART which was far beyond the capacity of the central hospital. By 2005, new cases had to decentralize to health centres, with clinical work being undertaken by medical assistants, nurses and other health personnel which required extra clinical staff. In this manner, provision of ART required significant additional investments in terms of both finance and human capital (Philips, Zachariah et al. 2008).

Aside from quantity (number) of doctors and other health personnel, it has been shown that the prognosis of HIV patients is significant related to the experience and knowledge of prescribing clinicians (Kitahata, Koepsell et al. 1996); (Stone, Mansourati et al. 2001); (Landon, Wilson et al. 2003). The experiences and knowledge of doctors will vary even in the developed world as it has been shown that European physicians tended to start ART for HIV-infected patients at lower CD4 cell counts than that of American doctors (Valian, Moyle et al. 1994). Even in the same country where standard guideline was published, a study regarding French physicians has shown that three month after clinical recommendations for HAART were made public, disagreement between patterns of ART prescription in some complicated cases was identified (Landman, Moatti et al. 2000). In the USA, it appears to be that infectious disease doctors are more likely than the general internal medicine doctor to prescribe ART (Stone, Mansourati et al. 2001). In a middle-income country like Thailand, expanding antiretroviral treatment (ART) for children requires

decentralization of the ART programme implying that service provision is managed mainly by non-specialist doctors (Ponnet, Frederix et al. 2005). Structures of treatment guidelines and types of doctors providing ART will largely depend on the human capital available to the country and this will impose a significant impact on the prognosis of the patients.

Treatment for HIV requires knowledge updating to match the changes in field of HAART. In developed countries, many non-specialist physicians would seek advice from their specialist colleagues (Stone, Mansourati et al. 2001). Thus, regular training is a pre-requisite as HAART is rapidly changing (Souville, Msellati et al. 2003); (Katabira and Oelrichs 2007). Since the introduction of zidovudine in 1987, over 2,000 combinations of ARV regimens have been recorded (Ghani, Donnelly et al. 2003).

2.5.4 Underdeveloped health infrastructure

Best practices of ART come almost exclusively from developed countries and are derived from cumulative clinical trials and the experience of well-organized treatment centres. In most developed countries, antiretroviral therapy is provided through centres specializing in the care for people living with HIV/AIDS with highly experienced physicians and staff. The care utilized a wide range of ARV drugs and sophisticated laboratory techniques utilised by specialists as well as developed surveillance systems for drug resistance (Jaffar, Govender et al. 2005).

The standards and techniques utilised in resource-rich countries with access to comprehensive therapeutic monitoring are not easily matched in resource-limited countries (Gilks 2001); (Loewenson and McCoy 2004); (Jaffar, Govender et al. 2005). Current treatment models developed in wealthy countries therefore require simplification and decentralization. The challenges of ART delivery in resource-limited countries include ensuring uninterrupted drug supplies, laboratory capacity for CD4 monitoring, accessible

voluntary counselling and testing (VCT), trained healthcare staff and effective monitoring of resistance to antiretroviral drugs (Loewenson and McCoy 2004) The optimum point to start HAART in developed countries is based on laboratory tests such as CD4 cell count and viral load (Aboulker, Babiker et al. 2004). In contrast, in resource-poor settings, CD4 cell count is likely to be the only option for initiating and monitoring the progress of HAART (Bogaards, Weverling et al. 2003).

Health systems in most developing countries are characterized by limited resources and services (Loewenson and McCoy 2004); (Jaffar, Govender et al. 2005); (Katabira and Oelrichs 2007). Jaffar suggested three requirements for the introduction of HAART programmes in such settings; (i) the possibility for health staff to look after the patients due to the shortage of doctors, (ii) possibility to deliver the care through the health peripheral health care system and (iii) an effective clinical algorithm to be used for screening, diagnosis case management (Jaffar, Govender et al. 2005).To expand the coverage of care required to meet the large number of PLHA, peripheral health facilities must take a major role in a decentralized structure of services to meet the needs of people in rural areas. The distance and cost of transportation to specialist centres located in towns and cities would be likely to result in reduced compliance (Jaffar, Govender et al. 2005). Providing care through peripheral health facilities such as health centres then would be likely to improve access to care. Peripheral health facilities, however, are often poorly equipped and overburdened by the demands placed upon them. Standardization of these facilities to deliver HAART is not easy and such a model of care is not likely to be feasible for doctor to deliver care due to the limited supply of health staff especially doctors or even nurses. Thus there is a role for trained health workers to undertake screening, counselling, monitoring and managing of adverse events for HAART care. In such circumstances, it is vital that this structure of care is evaluated and assessed to identify the clinical and cost-effectiveness of care provision.

2.5.5 Prevention

Prevention is still required to contain the epidemic of the disease; however, an effective HIV/AIDS vaccine is not envisaged in the near future. With comprehensive prevention (including twelve prevention interventions and nine care and support activities), it has been estimated to potentially save 29 million out of 45 million new cases that were projected to occur in this decade (Stover, Walker et al. 2002). Unfortunately, it was estimated that less than one in five people globally have access to such preventive services (UNAIDS 2004). Ensuring that prevention is comprehensive and interweaves a variety of interventions (e.g. voluntary counselling and testing, AIDS education, promote condom use, behaviour change programme, community education and prevention of mother-to child transmission) is still essential. Lack of prevention measures is highly associated with HIV/AIDS epidemic. For instance High risk-behaviours such as injecting drug use, unprotected paid sex and unprotected sex between men are found to be an important cause of epidemic in Eastern Europe, Asia and Latin America (UNAIDS 2006). Moreover, even where comprehensive prevention is encouraged, the prevalence of unprotected sex is showing an upward trend. For instance, UNAIDS has reported rates of 10%-20% of unprotected sex amongst groups of men who have sex with men (UNAIDS 2006).

Prevention is also considered to be a more cost-effective intervention compared with antiretroviral treatment (Creese, Floyd et al. 2002); (Marseille, Hofmann et al. 2002). For instance, a systematic review by Creese et al showed that many HIV preventive interventions (such as targeted condom distribution with treatment of sexually transmitted diseases, single-dose nevirapine and short-course zidovudine for prevention of mother-to-child transmission and voluntary counselling and testing (VCT)) together with tuberculosis treatment were cost-effective in African countries while HAART, home care programme and formula feeding for infants were considered less cost-effective (Creese, Floyd et al. 2002). It was, thus, suggested that prevention was the most cost-effective option for African

countries. Such results are largely explained by the fact that (i) primary prevention is easier, less costly, and yields more lives saved (ii) studies undertaken in the early HAART era utilised costs of antiretroviral (ARV) drugs that were relatively high compared to their present lower cost. In addition, there is the ethical dilemma that, irrespective of cost-effectiveness, it is difficult for policy makers not to offer known effective intervention such as ART to HIV infected people. This demonstrate the disadvantage of ranking programs according to the cost-effectiveness ratio which might aggravate disparities in access to treatment (Birch and Gafni 1992).

Table 2-5: Summary of meta-analysis of relationship between HAART and sexual health risk

Objective	To determine whether being treated with HAART, having an undetectable viral load, or holding specific beliefs about HAART and viral load are associated with increased likelihood of engaging in unprotected sex
Systematic review summary	▪ 25 English-language studies were identified and examined the association of unprotected sexual intercourse or STIs with receiving HAART (21 findings), having an undetectable viral load (13 findings), or beliefs about HAART and viral load (18 findings). ▪ The prevalence of unprotected sex was not higher among PLHA receiving HAART vs. those not receiving HAART (OR= 0.92; 95% CI= 0.65-1.31) or among PLHA with an undetectable viral load vs. those with a detectable viral load (OR, 0.99; 95% CI, 0.82-1.21). ▪ The prevalence of unprotected sex was elevated (OR, 1.82; 95% CI, 1.52-2.17) in PLHA, HIV-negative, and unknown serostatus persons who believed that receiving HAART or having an undetectable viral load protects against transmitting HIV or who had reduced concerns about engaging in unsafe sex given the availability of HAART comparing to the counter parts
Reviewers conclusions	HIV-positive patients receiving HAART did not exhibit increased sexual risk behaviour, even when therapy achieved an undetectable viral load. However, people's beliefs about HAART and viral load may promote unprotected sex and may be amenable to change through prevention messages
Reference	Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behaviour: a meta-analytic review. *Jama* 2004;292(2):224-36.

Concern has been expressed that the use of HAART may cause higher prevalence of unprotected sex and higher incidence of sexually transmitted diseases (STDs) (Huebner, Rebchook et al. 2004); (Behjati 2006). In one systematic review regarding sexual behaviour after the use of HAART, it has been shown that being prescribed with HAART was not associated with engaging in unprotected sex (see Table 2-5). Moreover, it was found that there was no association between undetectable viral load and sexual risk behaviour (Crepaz, Hart et al. 2004). However, in this study, all identified literature were from westernized

countries (16 of 25 from the USA), making generalisation of the findings to resource-poor settings difficult.

A study from Taiwan published in the same year has suggested that since 1989 in Taiwan, the infection rate of HIV decreased by 53%. However, this study was conducted in a specific setting where HIV prevalence is very low (0.19%) with extensive screening programmes (more than 20 million anti-HIV screenings in 22 million person were conducted during 1984-2002) (Fang, Hsu et al. 2004). Despite this success, a continuous effort to bring down the transmission rate of HIV is required even through the affect of HAART on risk behaviour in the long run seems to be minimal.

2.5.6 Adherence

As the cost of the treatment is relatively high, compliance becomes crucial. However, no gold standard for measuring compliance has been derived (Miller and Hays 2000). In general, subjective measures are cheap but tend to overestimate compliance while electronic measures provide greater information but at higher cost (Miller and Hays 2000).

Non-adherent patients place both themselves and public health at risk; as they are also less likely to adhere to drug toxicity screening. As the number of drugs increase due to the progression of the disease, there becomes a greater probability of developing adverse drug reactions (Sollitto, Mehlman et al. 2001) which may cause patients to abandon the treatment. One of the greatest concerns regarding non-adherence is drug resistance to one PI or NNRTI in the treatment regimen, causing treatment failures, leading to resistant viruses being passed on to sexual partners, people who share needles and others (Sollitto, Mehlman et al. 2001). In one review in 2000, it was shown that only an intensive pharmacist-led intervention consisting of educational counselling and availability of follow-up telephone support with conventional dispensing of HAART can significantly improve adherence and

subsequently predict undetectable viral load at 24 weeks (Haddad, Inch et al. 2000). Such an intervention requires excellent infra-structure and trained personnel which are unlikely to be available in resource-poor settings.

Non-adherence is complex behaviour and multi-factorial (Walsh, Horne et al. 2001). A study HIV patients reported occasional non-adherence with various reasons up to 15 reasons in some cases; the higher the number of reasons for missed doses, the lower adherence was observed (Walsh, Horne et al. 2001). The barriers to adherence were categorized into four themes (Alfonso, Bermbach et al. 2006); (Alfonso, Geller et al. 2006)

(i) Medication factors i.e., adverse effects, regimen complexity, dietary requirement. This is also the leading cause of non-adherence

(ii) Mood; distressing emotion such as depression, anxiety and anger could discourage some participants to adhere to the medication

(iii) Lack of support; the stigmatization of having HIV could cause some patients to decline ART

(iv) Outcome expectation as some of the patients did not believe in the efficacy of HAART

The threat of social stigma may also prevent PLHA from disclosing their status and thus presents a barrier to compliance with HIV treatment (Rintamaki, Davis et al. 2006); (Ware, Wyatt et al. 2006); (Rao, Kekwaletswe et al. 2007). However, the positive effect of HAART has, to a limited extent, alleviated the problem of stigmatization as HAART was found to be associated with less fear of HIV-infected people (Herlitz and Steel 2001). A small Brazilian qualitative study has also shown that stigmatization of HIV infection in children could be alleviated by universal access to HAART (Abadia-Barrero and Castro 2006). It is important to deliver the right message, particularly to the younger population who tend to receive less information compared to the older population (Herlitz and Steel 2001).

Retention rate in the programme is another simple way to measure adherence. Retention rates in ART programmes range between 25-44% (d'Arminio Monforte, Lepri et al. 2000); (Ahdieh Grant, Silverberg et al. 2001); (Dorrucci, Pezzotti et al. 2001); (Barron, Cole et al. 2004) with causes of low retention being similar to those of poor adherence. In terms of biological factors, a study identified patients with compromised immunologic status (low CD4 cell count) were at greater risk of dropping out from treatment (Brown, Thorne et al. 2006); (Protopopescu, Marcellin et al. 2007). Another study suggested that patients who stopped the treatment were likely to have lower health-related quality of life (Protopopescu, Marcellin et al. 2007). One study identified three reasons for non-adherence; (i) perceived necessity for HAART, (ii) concerns about potential adverse effects of taking HAART and (iii) satisfaction with perceived personal control over the decision (Cooper, Buick et al. 2002). This suggests that supporting informed decision-making regarding HAART is important from the beginning as it is important that patients feel in control (Cooper, Buick et al. 2002). The infrastructure should then ensure that such control continues throughout their treatment (Gebrekristos, Mlisana et al. 2005). In fact, HIV infected patients are generally actively involved with their providers as partners in decision-making (Marelich, Johnston Roberts et al. 2002). The four patterns of PLHA participation with providers about ART decision making were; (i) joint decision making between patients and providers, (ii) patients taking control of their drug treatment decisions, (iii) initial passivity followed by increased involvement, and (iv) patients as knowledge gatherers (revealing where patients get treatment information) (Marelich, Johnston Roberts et al. 2002).

2.6 Development of Thai national antiretroviral therapy programme

2.6.1 The epidemic of Thai HIV/AIDS

Thailand is one of middle-income countries in the problem growing region of Southeast Asia (UNAIDS 2004). HIV/AIDS has been prevalent in Thailand for more than two decades. The Thai responses to the problem have been changed gradually to match

situations in the country as global knowledge of managing HIV/AIDS problem has been growing. The first case of AIDS was diagnosed in Thailand in September 1984 and it was declared as the severe communicable disease since then (Thanprasersuk, Lertpiriyasuwat et al. 2004); (Ana Revenga, Mead Over et al. 2006). At the early stage, the disease confined itself to homosexual (1984-1987) male which later followed by the explosive spread of HIV infection among intravenous drug users (IVDUs) in 1987-1988 (Thanprasersuk, Lertpiriyasuwat et al. 2004). The disease, then, spread to commercial sex workers and their clients. With the heterosexual transmission route, reported of mother-to-child transmission started increasing during 1990-1991 (Thanprasersuk, Lertpiriyasuwat et al. 2004). It was estimated that by the end of 2008, more than a million of Thais will be infected with HIV since the first epidemic in Thailand, half of them already died. This will leave approximately 532,522 Thais living with HIV/AIDS in the year 2008. It has also been estimated that there would be 12,787 new infected cases which tends to be lower comparing to the previous years, and 50,657 new AIDS cases at the end of year 2008 as patients live longer from better HIV/AIDS carer (UNGASS 2008) (see Table 2-6).

Table 2-6: Estimated cumulative numbers of HIV/AIDS in 2008

HIV/AIDS	Cumulative number
Total HIV infection (adults and children)	1,115,415
Total death (adults and children)	585,830
People living with HIV	532,522
New HIV infection in 2008	12,787
New AIDS cases in 2008	50,657
Number of death from AIDS	26,935

Source: UNGASS country progression report: Thailand, 2008

2.6.2 Government responses to HIV/AIDS

The National Thai AIDS committee was established in 1985. At the beginning, its tasks were mainly for public health education, prevention and control and disease surveillance among target groups. AIDS prevention policies were described on availability of free condom, testing and counselling with confidentiality and anti-discrimination. Non

Government Organisations (NGOs) were also running their activities for prevention which funded by international agencies.

In 1987, the Ministry of Public Health expanded its coordination with NGOs under the National Advisory Committee on AIDS. In 1988, WHO initiated technical and financial support for the development and implementation of short-term HIV/AIDS plan. This was followed by the Thai Cabinet approval of the Plan for the Prevention and Control of AIDS (1989-1991). In 1990 the Thai Cabinet announced the official campaign against AIDS by making AIDS prevention and controls a national policy.

In 1991, the Prime Minister appointed the National AIDS prevention and Control Committee which resulted in multi-sector collaboration establishment. The campaign for AIDS prevention and control was launched in that year which involved with two key components including reducing the occurrence of male patronage of commercial sex workers and improving the safety of the commercial sex trade by means of condom utilization, termed the 100% Condom Programme (Buckingham, Meister et al. 2004). The mass media and advertisement played an important role in creating awareness for prevention of HIV/AIDS.

The government started allocated budget to the Ministry of Public Health (MOPH) to fight against AIDS in 1988 with the total money of $US 184,000 and reached $US 7.3 million in 1991 (Thanprasersuk, Lertpiriyasuwat et al. 2004). However, since 1992, the government budgets on HIV/AIDS were distributed through up to 14 Ministries and reached the highest in 1996 with the total amount of $US 80 million. In year 2004*, $US 40 million were spent for HIV/AIDS activities. Of $US 32 million (80%) were for the Ministry of Public health

* Exchange rate was approximately THB 25/ $US before 1997; and THB 40/$US after that year

and mainly for antiretroviral therapy. In total, it was estimated that more than $US 1.1 billion were already allocated from the national budget to fight again HIV/AIDS (Thanprasersuk, Lertpiriyasuwat et al. 2004).

2.6.3 Prevention

Without the remarkable success on prevention programme in the past of Thailand, it was estimated that Thailand would have to spend $US 18.6 billion in 2012 for treating HIV/AIDS patients. For every dollars invested in prevention, it yielded $US 43 can be saved for treatment expenditure (Ana Revenga, Mead Over et al. 2006). Thus, possibility of scaling up of antiretroviral therapy programme in Thailand is ground on the past successful effort on HIV/AIDS prevention (Over, Revenga et al. 2007). Without the multi-measure prevention, it was estimated that it would be as many as 7.7 million HIV-infected people and up to 850,000 AIDS cases in Thailand (Brown and Peerapatanapokin 2004). Comparing to the figure in Table 2-6 presented earlier, it is about 7 times more for HIV-infected cases and 14 times higher for AIDS cases. The effort of prevention has started since 1990; HIV/AIDS warning messages were publicized through all kinds of media including televisions, radio, posters and leaflets. They were aired regularly and repeatedly on television as part of the national strategy to minimize transmission of HIV. In 1991, all government-sponsored sexually transmitted disease (STD) clinics began to promote condom use. The "100% condom program" enlisted the cooperation of sex workers to encourage all clients to use condoms when having sex with the supply of 60 million condoms a year by the government (Lyttleton 1996); (Phoolcharoen 1998); (Svenkerud and Singhal 1998). The changing epidemic of HIV infection in the general population has been exhibited; (i) the Royal Thai Army's information on the HIV infection rate among its 60,000 annual military conscripts, selected by a draw from 21-year-old Thai males stated that the rate started to incline from 0.5% in 1989 to a peak of 3.7% in 1993 before declining at 1.9% in 1997 (Institute 1998), (ii) the sero-surveillance tests conducted on samplings of pregnant women in all 76 provinces yearly since 1989 also showed that rate of HIV infection was 0.5% in

1990, then increased to peak at 2.4% in 1995, and declined to 1.7% in 1997 (Health 1998), (iii) a cohort of repeat blood donors in the Northern Thailand, incidence rate had decreased from 1.7 per 100 person-years in 1989 to 0.5 per 100 person-years in 1994 (Sawanpanyalert, Yanai et al. 1996) . However, recent surveillance report form Ministry of Public Health Thailand, it found that risk behaviour such as having sex with commercial sex workers, low percentage of regular condom use were reports higher among military conscripts and married conscripts in 2003 (Health 2006). Comprehensive prevention is, thus, still needed in Thai society even though the number of new HIV cases is going down at present.

2.6.4 Multi-sector response to HIV/AIDS

Since the first epidemic of HIV/AIDS in Thailand, A major contributor to the problem has been the willingness of the government to alter strategies and policies as knowledge of the extent of risk behaviour grew and the social, economic, and cultural roots of the epidemic were understood. This willingness helped to identify the role that each sector of Thai society to response. Thus, the response of HIV/AIDS has been expanded from the public health sector to the social and economic sectors. The strategic alliances have included NGOs, private businesses, and community organisations that have worked as partners with the government (Phoolcharoen 1998); (Lyttleton, Beesey et al. 2007). The roles of PLHA activists have been recognized especially their legal and political advocacy in expanded ARV provision in Thailand (Lyttleton, Beesey et al. 2007). Networks of PLHA confront new social and political challenges as they also seek to broaden access for marginalised groups who remain excluded from these services. Many ethnic minority groups without full Thai citizenship have been denied access to subsidised health services including ART. As part of a broadening advocacy profile, the PLHA movement is now engaging in a politics of difference defined not simply by presence or absence of HIV but also by wider issues of national identity and belonging (Lyttleton, Beesey et al. 2007). Among all, the MOPH has played the key role in term of main strategic implementer and programme coordinator.

There has also been an evolution in the cooperation efforts from international agencies to government and local funding which is shown in Table 2-7.

Table 2-7: Roles of international and local organisations

Organisation/Group	Cooperation efforts
Department of Disease Control, Ministry of Public Health	1. Multi- working groups e.g. working group for antiretroviral therapy guideline development, working group for comprehensive care programme and working group for monitoring and evaluation 2. Scaling up and implementation of the government antiretroviral therapy programme throughout Thailand 3. Coordinating of antiretroviral programmes existing in Thailand 4. Monitor and evaluation of the government antiretroviral therapy programme
Office of Disease control in 12 regions of Thailand, Ministry of Public Health	1. Building up the antiretroviral therapy team for providing the care in their response areas 2. Monitoring and evaluation of the programme in their response areas
Government Pharmaceutical organisation (government enterprise)	1. Developing new generic antiretroviral drugs especially fix-dose combination of triple therapy 2. Manufacturing of antiretroviral drugs
Bumrasnaradura institution, Ministry of Public Health	1. Collaborating centre of WHO 2. Clinical management centre of Ministry of Public Health
People living with HIV/AIDS (PLHA)	1. Networking among themselves as part of care provider 2. Providing health education among group of PLHA 3. Being part of home visit team
NGO and international organisation♣	1. Involving in policy making process 2. Negotiating of antiretroviral drug price 3. Developing antiretroviral therapy guideline 4. Setting up campaign for treatment accessibility to needed people 5. Networking with people living with HIV/AIDS, NGOs and the government
Research institute	1. Conducting research base on the Thai context 2. Support antiretroviral drug free of charge 3. Providing technical support of implementation and expand of the antiretroviral therapy programme 4. Developing monitoring and evaluation tool for antiretroviral therapy programme

Source: Bureau of AIDS, Tuberculosis and Sexually Transmitted Infection, MOPH, 2004

Another important party in the Thai context of HIV/AIDS care is PLHA self-help groups especially in the rural areas. It was estimated that more than 920 groups existed in 2006

♣ NGOs and international organisation including World Health Organisation/the Joint United Nation Programme on HIV/AIDS (WHO/UNAIDS); Thailand MOPH-U.S. CDC Collaboration (TUC), Global Fund to fight HIV/AIDS, Tuberculosis and Malaria, Japan International cooperation agency (JICA), Oxfam, Medecins Sans Frontieres (MSF), Access Foundation, Thai NGO's coalition on AIDS (TNCA), Thai Network for People Living with HIV/AIDS (TNP+)

(Lyttleton, Beesey et al. 2007). In the early stage most of the group were concentrated in Northern Thailand as to the response to the epidemic of HIV and mostly were hospital-based under the encouragement of hospital staff. At first their activities focused on income generation, moral support for public disclosure of HIV status and self-care. They also provide voluntary support which closely linked to the provision of ART for PLHA such as training courses on various opportunistic infection and comprehensive care to members of PLHA groups, the major component of holistic care, promote adherence as who will be lost to follow up will be visited by the member of the group. Later the groups have meshed with each other and become a network linking at sub-district-, district-, provincial-, regional- and national-levels to increase social and politic advocacy which further the access to ARV drugs as well as opportunistic infection prophylaxis to the underserved group in Thailand (Lyttleton, Beesey et al. 2007).

2.6.5 Evolution of antiretroviral therapy in Thailand

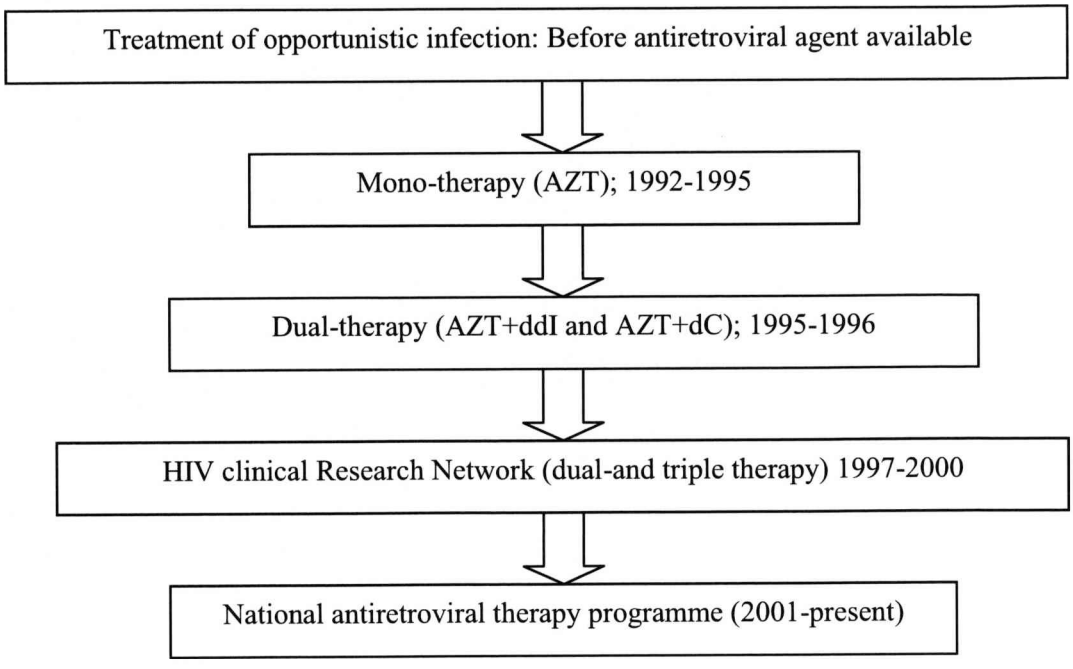
2.6.5.1 Initial stage of antiretroviral therapy

Since the first identified case of HIV/AIDS in Thailand in 1984, the subsequent response from all segments of government and Thai society helped to deal with the epidemic of HIV/AIDS. In 1991, zidovudine (AZT) was firstly distributed to AIDS cases. The Ministry of Public Health had proposed the drug to be included into the National Drug List. Number of cases with single therapy with AZT was rising from 15,000 cases in 1994 to 45,000 cases in 1995 (Thanprasersuk, Lertpiriyasuwat et al. 2004). Most of the cases were in either referral centres or university hospitals. The treatment programme with AZT was later evaluated by World Bank, WHO and the Ministry of Public Health (MOPH) in 1995, the evaluation showed no evidence of clear survival benefit and high proportion of patients lost to follow-up (Prescott N 1996). The government, then, decreased the budget for AZT and reallocated the budget for clinical trials network by the Ministry of Public Health instead (Phanuphak 2004).

The evaluation by World Bank and WHO also stated that AZT for preventing mother-to-child transmission would be more cost-effective which corresponded with both Thai and international studies showing the effectiveness of AZT reducing mother-to-child transmission rate (Sperling, Shapiro et al. 1996); (Thaineua, Sirinirund et al. 1998); (Shaffer, Chuachoowong et al. 1999); (Lallemant, Jourdain et al. 2000). The Ministry of Public Health firstly implemented a short regimen of AZT to all consent HIV-infected women to prevent mother-to-child transmission (PMTCT) of the virus through seven public hospitals in Phayao province, Northern Thailand (Thaineua, Sirinirund et al. 1998) in 1997. At the same time, Glaxo Wellcome reduced 75% of the original price of AZT to $US 100 per case (Baker 1998). Since year 2001, the programme to prevent mother-to-child transmission has been available throughout public hospitals free of charge (Kanshana and Simonds 2002); (Phanuphak 2004); (Thanprasersuk, Lertpiriyasuwat et al. 2004).

The Clinical Research Network for antiretroviral therapy was established in 1996 including 58 referral and university hospitals. In 1998, treatment with two antiretroviral agents (dual therapy) was used as the standard treatment. However, only 1,200 patients benefited from this research programme (Thanprasersuk, Lertpiriyasuwat et al. 2004). With high demand for antiretroviral and high cost of the drugs, co-payment which requested patients to partly pay for the expensive drugs such as non-nucleoside reverse transcriptase inhibitors and protease inhibitors was initiated in 2000. Still, only few hundred of people participated in the scheme (Thanprasersuk, Lertpiriyasuwat et al. 2004).

Figure 2-6: Access to HIV/AIDS medical care in Thailand



Source: Ministry of Public Health, Thailand

2.6.5.2 National government antiretroviral therapy programme

The development of ART implementation as the national programme under the universal coverage health scheme has been started since 2001 (Chasombat, Lertpiriyasuwat et al. 2006). In that year, national antiretroviral therapy programme called "Access to Care" was initiated by the Ministry of Public Health. Eight HAART regimens for adult and 12 regimens for children were prescribed to eligible participants. However, the programme was limited in hospitals where a trained staff team for ART were available (Thanprasersuk, Lertpiriyasuwat et al. 2004). In 2002, the generic local made GPO-Vir with fix-dose regimen was produced by the Government Pharmaceutical Organisation (GPO) at a cost of $US 1 per person per day. It was the combination of 3TC (lamivudine) +d4T (stavudine) +NVP (navirapine). Since the second year of the national antiretroviral therapy programme (Ford, Wilson et al. 2004); (Phanuphak 2004), the programme recommended GPO-Vir as the first-line regimen. In 2003, the government by the Ministry of Public Health aimed to expand the treatment programme to cover every needed individual. The programme title

was changed to "National Access to Antiretroviral Programme for People who Living with HIV/AIDS" (NAPHA).

The number of patients who benefit from the government ART programme has been increase from 3,600 in 2001 to 23,000 in 2002 (Panpanich 2004). The people were entitled to the programme under the universal health scheme, the civil servants' welfare or social security scheme. Training for relevant medical personnel including doctors, nurses, pharmacists, laboratory technicians, counsellors and social workers was carried out in every region of Thailand. Number of hospitals involved in the programme had gradually expanded from 112 hospitals in 2001 to 462 hospitals in early 2003 and reached 841 by February 2005 (Thanprasersuk, Lertpiriyasuwat et al. 2004). Total number of patients recruited into the programme reached the total of 13,000. In 2004, the programme was expanded to cover as many as 50,000 patients. The budget was four-fold increase compared to that of the year 2003 (Thanprasersuk, Lertpiriyasuwat et al. 2004). As on May 2006, the World Bank report has stated that approximately 77,758 people were receiving through the national ART programme, nearly 8,000 were accessed via the Social Security Scheme (SSS) (Ana Revenga, Mead Over et al. 2006). In total, it was estimated that 61% of people living with AIDS in Thailand are receiving the ART as on 2007 (UNGASS 2008).

The government antiretroviral therapy is mainly delivered through public facilities including district, general (provincial), regional and some university hospitals. Generally, the antiretroviral (ARV) clinic is ambulatory which serves as a part of out-patient department in a hospital. In large hospitals such as general, regional and university hospitals, care is usually provided by doctors as the first contact. On the other hand, in district hospitals, ARV clinics are either run by doctors or nurses. In case where nurses are the first contact of services, complicated cases are handed over to doctors. It was estimated that by the end of 2004, there were 800 antiretroviral sites to provide care throughout Thailand (Phanuphak

2004). In Chiang Mai, Northern Thailand, antiretroviral therapy delivery at health centres under supervised of district hospital for uncomplicated cases is also being initiated. Moreover, to reach the HIV-infected children the national ART programme has tailored the guideline and recommendation specific to children and programme for children has been run side by side with the adult programme. In recent evaluation, it has found to be the treatment is as effective as that found in the adults after 72 weeks of treatment in term of virological and immunological response (Puthanakit, Oberdorfer et al. 2005)

2.6.5.3 Production of generic antiretroviral drug

High cost of the antiretroviral drugs was once considered as a major obstacle for antiretroviral drug accessibility. Regarding this problem, the Thai government by GPO began to conduct researches and developed antiretroviral drugs in 1992. It started first with Zidovudine (AZT) and Dideoxypurine nucleoside (ddI). The generic of AZT was later produced in 1996; however, generic production of ddI was blocked by the patent hold company- Bristol Myers-Squibb (BMS). In November 1999, the GPO submitted a request for a compulsory license to override the patent to produce a generic ddI to the Thai Department of Intellectual Property. The use of compulsory license was prohibited. In year 2002, the network of Thai people who living with HIV/AIDS won a lawsuit against BMS which claimed that the BMS patent registration for its buffered tablet formulation of the ddI (brand name Videx) was illegally amended in an attempt to claim for a wider monopoly than the patent description justified (Ahmad 2002); (Kapp 2003). Thus, the Government Pharmaceutical Organisation can legally produce alternative form of ddI at the lower cost compared to the imported Videx. This was coordinate with World Health Assembly in 2003 which emphasized on making vital drugs including antiretroviral drug available to the people at affordable cost (Kapp 2003). In 2002, the first fix-dose generic antiretroviral drug produced in Thailand called "GPO-Vir" was produced. The evidence of its efficacy was confirmed by one study which found that GPO-vir was well tolerated and effective in

increasing CD4 cell counts and suppressing plasma viremia in advanced HIV infection during the 48 weeks follow-up period (Getahun, Tansuphasawadikul et al. 2006). The present lists of drug price in Thailand are shown in Table 2-8.

Table 2-8: Cost of ARV drugs per patient by regimens in Thailand

Antiretroviral regimen	Month cost per person ($US)	Annual cost per person ($US)
First-line regimen (MOPH guideline)		
(1) 3TC+d4T+nevirapine	30.0	360.0
(2) d4T+3TC+efavirenz	64.5	773.7
AZT+3TC+efavirenz	95.5	1,145.7
AZT+3TC+nevirapine	60.0	720.0
(3) d4T+3TC+IDV/r	87.5	1,050.0
AZT+3TC+IDV/r	118.5	1,422.0
Second-line regimen		
ABC+ddI+LPV/r	570.6	6,846.6
ABC+ddI+SQV/r	552.4	6,628.2

Source: World Bank: The economics of effective AIDS treatment: Evaluating policy option for Thailand

2.6.5.4 Financing of ART

In early stage of antiretroviral drugs in Thailand, people who required for the treatment had to pay for the antiretroviral drugs. The high medication costs brought down the accessibility to the drugs. Efforts to lower down the drug price were made by the government together with NGOs. However, not many people can access to the drugs and free of charge ART programme can be benefit limited to some people who can access to the free programme providing NGOs or research institutes in some areas of Thailand. The government supported ART at the initial stage was also considered as research programme.

In one micro-costing study in Khon Kaen, Thailand during the period of 2001-2002 before the nationwide ART scale up, it was found that the average cost per outpatient visit with and without antiretroviral drugs was $US294.2 and $US26.1, respectively. The average cost per inpatient day with and without ARV drugs was $US368.1 and $US43.8, respectively. The net annual cost of HAART was estimated to be $US5 674 629. This is equivalent to 20.0% of the annual budget for the health scheme for adults in Khon Kaen in 2002. The huge differences between costs of patients with HAART and without HAART was due to that the

study was conducted before the invention of generic locally produced ARV in Thailand (Kitajima, Kobayashi et al. 2003). Thus, the major of the costs component for those who on ART was costs of the brand name drugs which drove the cost in those who one ART ten times more expensive than those who were not taking the drugs.

Aside from either full self-pay or free drugs programme, partly pay for the drug or co-payment was also initiated in 2000. The programme turned the patients from drug receivers to co-providers. This project was run by the network of people living with HIV/AIDS (PLHA) in Thailand with supports from AIDS Access Foundation and Medecins Sans Frontieres (MSF) called the buyer club. The club dealt directly with Government Pharmaceutical Organisation to purchase generic antiretroviral drugs as well as the some imported drugs such as Efavirenz which hold patent protection in Thailand. Patients were prescribed medication by doctors in public hospitals, then, they usually took the prescription to the club which dispensed the medicines together with treatment information, counselling and assisting in dosage planning as well as the follow-up time schedule. The central stock was held in the Thai Networks for people living with HV/AIDS (TNP+) office in Bangkok, Thailand. Up till June 2002, there were 21 Buyer's Club branches and 1,081 people on the treatment. However, the number of the patients in this programme had been declining due to expansion of the free government programme. New cases would benefit from the free government programme and the non-naïve cases also switched to the government programme which now accepts previous treated patients (Ana Revenga, Mead Over et al. 2006).

The government programme which providing antiretroviral care free of charge made an attempt to expand to cover every need. By the end of 2007, it was estimated that more than 61% of PLHA were able to access to the drugs (UNGASS 2008) under three major medical insurance schemes in Thailand; the Civil Servant Medical Benefit Scheme (CSMBS), the

Social Security Scheme (SSS) and the Universal Coverage Scheme (UCS). The first covers civil servants, government enterprises' employees and their family members; the second covers employees in formal sectors of private companies and the last covers the rest of population. However, self-pay is another option for people who seek for more cares rather than what they receive under their schemes and for those who have no insurance (Thanprasersuk, Lertpiriyasuwat et al. 2004). The national ART programme is still recruiting for more patients. With expansion of the government programme, the NGOs and research programme which provide free ART, then, has handover their cases to the government programme. Even the nature of free of charge programme, however, the government programme was not yet included into the basic service care package in the UCS (Thanprasersuk, Lertpiriyasuwat et al. 2004). This was because of the expected long-term cost and higher number of patients in the future. High future cost was the result of the fact that drug resistant is unavoidable, alternative prescribed regimen is usually more expensive. Thus, with limited government subsidy per capita to the care providers for providing cares in the UCS, this could cause the financial burden in the long-term. The present overall annual cost per person of providing HAART has shown in Table 2-9.

Table 2-9: Annual cost per patient by antiretroviral regimens

Cost component	Annual cost per person ($US)	
	First-line regimen	Second-line regimen
(1) ARV drugs	471.2	6,589.2
(2) Laboratory tests	30.3	30.3
(3) OI infection	120.4	120.4
(4) OPD service	69.3	69.3
(5) IPD service	151.0	151.0
(6) ARV+Laboratory test (1)+ (2)	501.4	6,619.4
(7) Hospital services (4)+(5)	220.4	220.4
(8) Total ARV cost (3)+(6)+(7)	842.2	6,960.2

Source: Supakankunti et al 2004

A recent report from the World Bank has suggested that the first-line regimen recommended by the MOPH (See Table 2-9) was the most cost-effective option for Thailand; at a cost of $US 736 per discounted life-year saved compared to $US2,415 per discounted life- year saved for that of second-line regimen (Ana Revenga, Mead Over et al. 2006). However, the

second-line regimen was still affordable and brought in subtle benefits in relation to life year saved (Ana Revenga, Mead Over et al. 2006). In the projection by the World Bank, the Thailand's AIDS spending will increase from $US100 million per year to more than $US500 million per year by the year 2020 due to the switch to use second-line drug regimen. Moreover, in this report, it has been showed that the public financing of ART will help ensure equitable access especially when the second-line treatment is of use (Ana Revenga, Mead Over et al. 2006). In overall, with the life-prolonging effects by HAART the number of ones who need the treatment will increase as well as the more complex and more costly treatment in the future, the forthcoming AIDS cares expense could rise substantially (Nagelkerke, Jha et al. 2002). In overall, ART is thought of as the cost-effectiveness in Thailand. From the projection using epidemiologic/economic model to 2025, the use of ART can save the money up to $US 3.2 billion. However, this depends on the use of local produced generic ARV (Ana Revenga, Mead Over et al. 2006).

Recently, a study explored the inequality in term of access to HAART in the Thai context has been published which showed that people with CSMBS were significantly likely to receive ART compared with patients under the UCS (Kitajima, Kobayashi et al. 2005). However, the number of study investigating the inequality in relation to benefit from HAART among social classes after the roll out of the free-of-charge national programme in Thailand is still relatively limited. The country, thus, requires insightful information for better equitable distribution regarding benefit of the programme in its own context for its own people.

2.7 Summary

(i) HAART is considered as the standard of care for HIV/AIDS treatment but few amounts of people in developing countries can access to the treatment.

(ii) Scaling up of the treatment has been increasing dramatically over the past few years with the great efforts from multi-organisation at both local and international levels, Most evidence in relation to treatment outcomes and experiences of ART are from developed countries. In contrast, only a little knowledge in this field is from developing countries where the majority of PLHA resides. Transferring of knowledge to this part of world requires cautious consideration.

(iii) Inequalities among social classes of people in relation to accessibility to the treatment and benefits of the treatment still exist in spite of availability of effective treatment and falling down on drug prices both in developed and developing countries

(iv) Factors determine success of the ART programme vary according to settings as well as its costs which cannot be directly transferred. Countries have to understand their own dynamics of ART programmes which are specific to the setting and would benefit people both domestically and globally. Given Thailand, which is the middle-income developing country, the model that is applicable in this setting might be able to generalise to other developing countries whereas model that is inapplicable in Thailand would be difficult to induct to other poorer setting.

(v) In Thailand where implementation of a national antiretroviral programme using its own produced GPO-Vir was officially initiated since 2003, patterns of HIV/AIDS cares are diverse, evidences of benefits of the programme in relation to mortality, disease progression and other outcomes are also limited. Moreover, benefit distribution in various social classes might vary from group to group. The exploration to have an insightful understanding of the programme regarding its characteristics and benefits to a variety of population is needed

For the next chapter, hypothesis and objectives are presented followed by the procedures to test the hypothesis and to accomplish the objectives of the present study. Study design, study sites, participants, outcomes measures and process of data collection and analysis are clearly stated in the next section.

CHAPTER 3
METHODS

3 Methods

In Thailand, it was estimated that 61% of PLHA are receiving ART through the national government antiretroviral therapy program since the start of the programme in 2001 (UNAIDS 2008). However, evidences of the impact of ART on survival and other outcomes such as health-related quality of life, as well as factors contributing the treatment outcomes in Thailand are still scarce.

In this chapter, the hypothesis which the researcher aimed to investigate, objectives of the present study, study design, main outcomes measured and the procedure of data collection as well as the data analysis are presented according to the objectives which are shown below

3.1 Hypothesis

Null hypothesis: there was *no association* between socioeconomic status (defining by household income) of the HIV-infected patients and their HIV-related mortality following enrolment into the Thai national ART programme"

Alternative hypothesis: there was an *association* between socioeconomic status of the participants and their HIV mortality following enrolment into the Thai national ART programme since the roll out of the government ART programme; anticipated that 20% of patient with household income equal or below the median would die while 10% of the patients with household income above the median would die

3.2 Objective

1. To determine the impact of ART on treatment outcomes in relation to:-
   i. Survival
   ii. Health-related quality of life
   iii. Immunologic response (CD4 cell counts)

iv. Duration of the first-line regimen of the ART

2. To explore factors that may contribute to the treatment outcomes, the factors include

v. Age

vi. Gender

vii. Socioeconomic status

viii. Education

ix. Health insurance

x. Accessibility to the hospital

xi. Being member of PLHA self-help group

xii. Being naïve to the ART

xiii. Baseline CD4 cell counts

xiv. Disease staging before starting ART (according to WHO classification)

xv. Initial prescribed regimen

xvi. Type of ARV clinic (nurse-led vs. doctor-led)

3. To explore the characteristics of PLHA who received antiretroviral therapy in relation to baseline characteristics and their clinical information and the experiences of care provided by different types of ARV clinic (doctor- and nurse-led clinic)

For terminology and definition used in this study, please see Annex-3 for more information.

3.3 Study design

This present study aims to identify the treatment outcome of HAART in those who initiated the treatment between March 1, 2001 and April 30, 2004. Thus, all those who started the treatment during this period (a total of 501 participants) should be included to avoid the selection bias.

During May-July 2004, a survey which was conducted to explore the characteristics of ART providers and PLHA who were initiated ART between March 1, 2001 and April 30, 2004

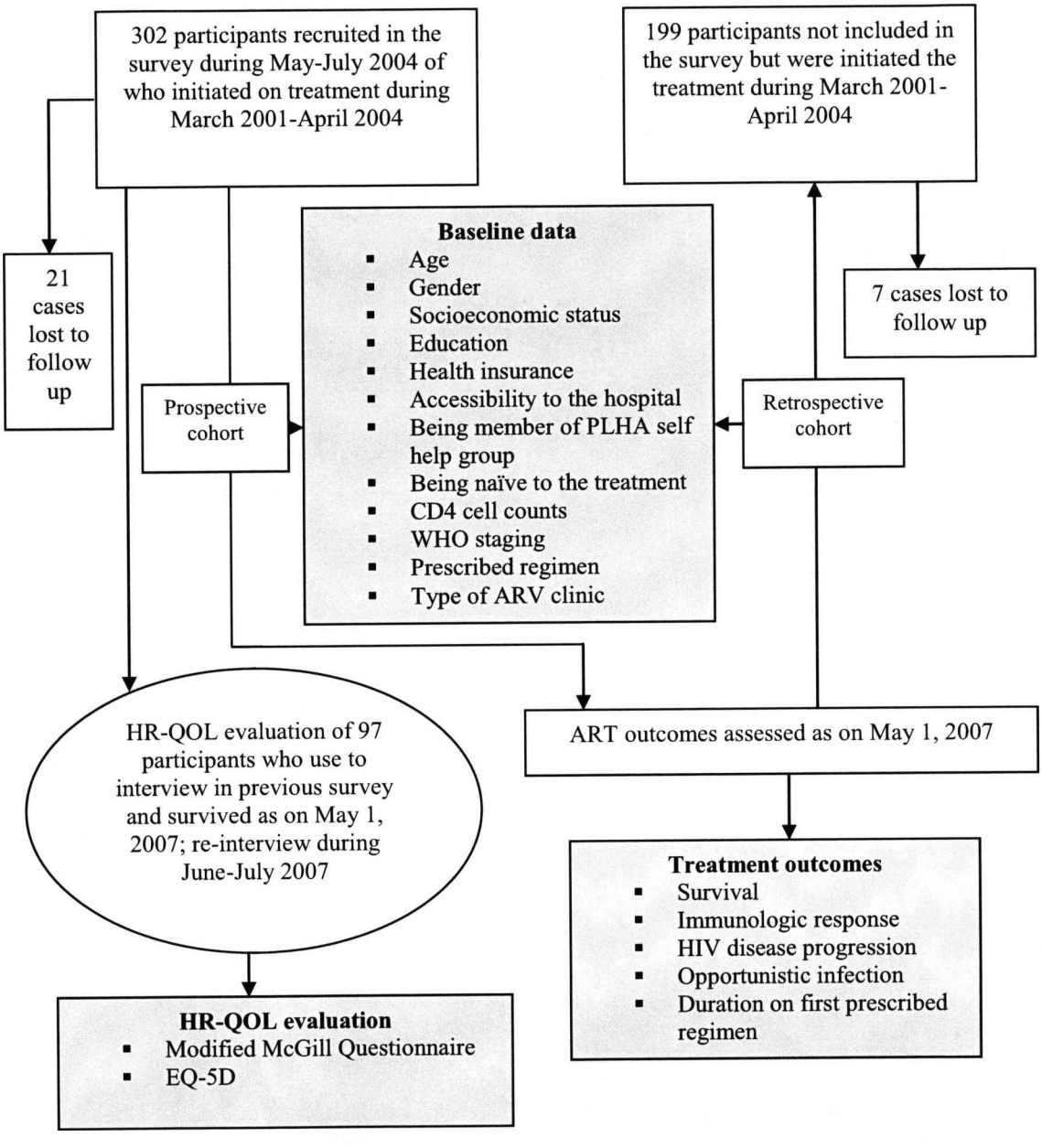
(Objective 3). To identify the treatment outcome in this group of patients, they were followed and assessed for the outcomes as on May 1, 2007. However, due to the sampling at that time, only 302 participants were included, thus, another 199 had to be sought. This was to identify the effects of ART on the outcomes of overall patients who started the treatment during that period as the survival which based on the prospective cohort alone would not be able to estimate the accurate survival

This survival study is then a combination of two cohorts (see Figure 3-1, study diagram) which are

(i) Prospective cohort; this section was conducted based on the survey in 2004. The participants in this group were followed and assessed for the treatment outcome on May 1, 2007. To identify the outcomes in relation to health-related quality of life, in this cohort, a subgroup of 97 participants who were interviewed in the survey were re-interviewed to evaluate for the changes of health-related quality of life over the three years period of ART. The re-interview was conducted during June-July 2007

(ii) Retrospective cohort; in this part of the study, the treatment outcomes of the patients who were not included in the prospective cohort but were initiated the treatment between March 1, 2001 and April 30 were sought as on May 1, 2007 (199 participants). And to identify factors that might influence the outcomes, baseline characteristics and clinical information of the participants in this group were also sought. Again, this cohort did not constitute part of the initial sample surveyed; the data on outcomes for this group are likely to be less reliable or valid as for the initial sample.

Figure 3-1: Study diagram



3.4 Scope of the study

This study aims to focus on identifying the impact of the ART on survival and other treatment outcomes including HR-QOL, improvement of the CD4 cell count and duration on the first-line regimen. The study also attempts to explore the association between those outcomes and patients' characteristics regarding socioeconomic, gender, accessibility, etc., of those who have entered into the national antiretroviral therapy programme in Chiang Mai, Northern Thailand in the context of universal health care setting since the rollout of the

programme in 2001. However, the researcher does not try to identify or assess factors determining access to the treatment programme.

3.5 Study sites

The government ART programme has been implemented throughout Thailand since 2003 under the universal health insurance scheme (Over, Revenga et al. 2007) and services of the programme has been delivered through various sizes of health facilities; from small units such as district hospital to large units like university hospital. However, the services have been provided mainly through hospitals under the Ministry of Public Health (MOPH) (Thanprasersuk, Lertpiriyasuwat et al. 2004); (Chasombat, Lertpiriyasuwat et al. 2006); (Thanprasertsuk, Lertpiriyasuwat et al. 2006). The services are also available in some private health facilities with partial support from the MOPH, but this is still uncommon (Thanprasersuk, Lertpiriyasuwat et al. 2004).

Figure 3-2: Map of Chiang Mai and Thailand

Source: http://www.bmair.nl/Informatie/Thailand/Kaarten/Kaart-Thailand-Chiang-Mai.gif **(Accessed April 2008)**

This study began firstly in 2004 in the area of Chiang Mai. It is the third biggest province in Thailand regarding its population (Thailand 2005). It is located in upper Northern Thailand which is about 750 kilometres away from Bangkok. Its population was 1.6 million in 2003 with slightly more of women to men. In relation to HIV/AIDS, Chiang Mai is only the second most affected area of HIV/AIDS to Bangkok since the beginning of the HIV/AIDS era. Up till March, 2008, there are about 21,915 cases reported form Chiang Mai which account for 6.6% of total AIDS cases in Thailand (21,915 out of 328,864 cases) and 21% of cases in Northern region (MOPH 2005). The incidence rate of AIDS cases has been

declining, however it is still relative high compared to nationwide incident rate; in 2004, the incidence rates of AIDS in Chiang Mai and Thailand were 38.8 and 32.0 per 100,000 population respectively and were 27.6 and 14.9 per 100,000 population in 2007 (MOPH 2005). According to what mentioned above, Chiang Mai was chosen by the Ministry of Public Health to pilot the national antiretroviral treatment programme 2 years prior to the rest of the country, thus, it has more experiences of ART and patients with longer follow up duration comparing to other places in Thailand (Thanprasersuk, Lertpiriyasuwat et al. 2004).

Table 3-1: Registered health facilities in Chiang Mai

Health facility	Number
Ministry of Public Health	
General hospital	1
District hospital	
▪ 120-bed	1
▪ 90-bed	2
▪ 60-bed	1
▪ 30-bed	14
▪ 10-bed	2
Health centre	255
Other Ministries	
Hospital	5
Private	
Hospital	13
Clinic	276
Dental clinic	64
Mid wife clinic	24
Drug stores	298

Source: Annual report of registered health facility in Chiang Mai year 2004 by Chiang Mai Provincial Health Office.

Table 3-2: Information about three selected ARV clinics in fiscal year 2003 (Oct 2002-Sep 2003)

Information	ARV clinic 1	ARV clinic 2	ARV clinic 3
Type of practitioner in ARV clinic	Doctor-led clinic	Large nurse-led	Small nurse-led
Number of responded doctors	1	2	1
Number of responded nurses	3	6-7	2
Number of patients in the government ART programme♠	163	218	94
Hospital type	General	District	District
Number of bed	531	120	30
Distance from Chiang Mai city centre (Km)	10	25	20
Year founded	1992	1982	1982
Number of hospital staff			
Doctors	66	12	6
Dentists	7	5	3
Pharmacists	23	8	5
Nurses	405	94	43
Other medical staff	558	31	66
OPD			
Number of patients	135,997	38,340	28,857
Number of visits	325,801	173,494	121,324
IPD			
Number of beds	531	120	30 (53)
Number of admissions	28,671	8,141	3,509
Number of in patient days	182,503	52,772	16,711
Number of deaths	1,125	93	19
Number of referrals	149	2,515	419
OR and LR			
Operations	13,878	987	40
Deliveries	1,804	332	189

Source: annual report of year 2003 of the three hospitals

3.6 Selected facilities

In Chiang Mai, general (provincial) and district hospitals have played an important role of the services delivery to promote the programme coverage especially to the outreach areas (see Table 3-1). The programme is usually delivered strictly through hospitals, however, the programme services for uncomplicated cases have been initiated in some well-organized sub-district health centres to reduce burden of workloads in the hospitals as well as to decrease waiting times and expenses of the patients as the health centres are usually located in the community and easier for patients to get services.

To demonstrate the delivery of ART in various types of health facilities in Chiang Mai, three ARV clinics from three hospitals were selected as the study units from the list of

♠ Information on July 31, 2004

hospitals operated under the Ministry of Public Health in Chiang Mai as public hospitals are the major provider of the government ART programme. One doctor-led ARV clinic in general hospital and two nurse-led ARV clinics (large and small clinics) from two district hospitals was included (see Table 3-2). Two different sizes of nurse-led clinics, which determined by number of patients registered to the clinics, were selected because different capacity of facilities would instigate differences of characteristics of the patients as well as effectiveness of the programme.

3.7 Participants

The participants were both men and women patients aged 18 or older who were treated with HAART in the government ART programme from the selected facilities. This study included all who initiated the treatment during March 1, 2001 till April 30, 2004. The calculation of the sample size was performed to test the study hypothesis; the computation was based on the association between socioeconomic status and mortality rate

Null hypothesis: there was *no association* between socioeconomic status (defining by household income of the participants) and their HIV-related mortality following enrolment into the Thai national ART programme since the roll out of the government ART programme.

Alternative hypothesis: there was an *association* between socioeconomic status of the participants and their HIV mortality following enrolment into the Thai national ART programme since the roll out of the government ART programme; anticipated that 20% of patient with household income equal or below the median would die while 10% of the patients with household income above the median would die

Calculation: using the EPI Info TM 2002, at the statistic significant level = 0.05; power = 0.8; ratio 1:1, with two sides test, total required sample size was approximate to 219 in each group (total required =438). However, this study would include participants up to 500 to allow the drop out.

[Alternative method use to calculate the sample size was shown in Annex 5]

Regarding the sample size, two methods to calculate the sample size were used to ensure that the required number of participants was adequate. However, the number was based on the projection of the mortality rates between two groups of household income in which no known data regarding this projection was available. Moreover, the participants were also recruited more than what calculated by two methods to increase the power of the study and allow for drop out of the participants from the study.

3.8 Data procedure

In the present study, the outcomes of the ART were assessed on May 1, 2007 based on the 501 participants from the two cohorts (prospective and retrospective; see section 3.3) who initiate the treatment during March 1, 2001-April 30, 2004. The data of the factors that might influence the outcomes were also collected based on the baseline characteristics of the participants.

(i) In the prospective cohort of 302 participants, it was based on a survey which was undertaken during May-July 2004, clinical information as well as baseline characteristics of patients were gathered. In relation to health-related quality of life, a subgroup of 97 patients of the prospective cohort was randomly drawn from the list of those who still survived and were interviewed for their HR-QOL in the survey in 2004. They were re-interviewed using the Modified McGill Questionnaire

and EQ-5D during June-July 2007 to evaluate the changes in their HR-QOL after the period of three years on HAART

(ii) For retrospective cohort, the treatment outcomes of 199 were followed up and were determined at the same time as the prospective cohort on May 1, 2007. Baseline characteristics and clinical information were also sought to identify their association with the treatment outcomes. Still, this cohort did not constitute part of the initial sample surveyed; the data on outcomes for this group are likely to be less reliable or valid as for the initial sample

The data procedures in the present study were separated regarding to these two cohorts.

3.8.1 Prospective cohort

3.8.1.1 Baseline data from the survey in 302 participants

This was the first part of the study which aims to understand the situation of national antiretroviral therapy programme after the roll out in Chiang Mai since 2001, and to retrieve the baseline characteristics, clinical information and their health-related quality of life of the participants. During the survey, clinical information of the participants was extracted while patients' characteristics were gathered using patient interviews

3.8.1.1.1 Medical record review

Medical record and the visit forms of each participant were reviewed and extracted. The retrieved clinical information included

(i) Age

(ii) Gender

(iii) Health insurance

(iv) Status before start the antiretroviral treatment (naive or experienced)

(v) WHO HIV/AIDS staging before initiation of ART

(vi) Date start the treatment

(vii) Duration of follow up at the clinic

(viii) Regimen of ARV used

(ix) Baseline CD4 cell counts, CD4 cell counts at 6- and 12-month after initiation of ART

(x) Baseline body weight, body weight at 6- and 12-month after initiation of ART

(xi) Initial prescribed regimen

Both extreme values and missing values were verified and sought before recording onto the excel spread sheet.

3.8.1.1.2 Questionnaire and patient interview

Information regarding patient characteristics, socioeconomic status, access to the hospital, and other related issue were identified by doing patient interviews. The interviews using structured questionnaire by trained interviewers in Thai language were performed. Please see Annex-4 for full questionnaire. The interviews were conducted during May-July 2004. Two to three volunteers PLHA in each hospital were trained to be the interviewers by the researcher. The interviews could be arranged to do in other places at other times at their convenience under the agreement and permission of the participants; the interviews could be carried out at patients' house and patients' working places. The given information from each participant was gathered and analyzed by the researcher

The interview took on average half an hour for each patient. The patients were informed of the rational, objectives, risks of the study, confidentiality as well as their right to participate and quit from the study before proceeding with the interviews. Possible risks from the interviews were minimized as much as possible. Clarifications were verbally provided by the interviewers when required.

The questionnaire was newly built. This structured questionnaire contained of both multiple-choice questions and some open-ended questions which covered the following nine main areas (see Table 3-3)

Table 3-3: Data from the interview of 302 participants during May-July 2004

Information	Description
Patient characteristic	Age, gender, religion, highest education level, type of health insurance, marital status, number of people in the household, number adult with HIV infection, number of children with HIV infected, number of treated with ARV
Socioeconomic status	occupation, main wage earner, income, household income, type of accommodation
Accessibility	distance, travelling time, method used to come to the hospital
Adherence	number of doses not taken within a week and number of doses not taken within a month, number of doses taken late then usual time more than 30 minutes within a week, number of doses taken late then usual time more than 30 within a month, last dose of drug not taken, reason not to take, any intention not to take the medicine, method use to remind taking medication, number of missed appointment within 3 months
Social issue and stigmatization	support from the PLHA self-help group, HIV status know by his/her couple, family, community , experience of people turn away,
Sexuality	Sexual activity within 3 months, number of people having sex within 3 months, usage of condom
Services at the ARV clinic	Time spent at the ARV clinic, feeling about time at the clinic, see doctor for the last visit, time spent with doctor, feeling about time spent with doctor, received information regarding ARV, feeling about information given, feel private enough in the room, conceived of dislike from hospital staff, hospital action when missed appointment
Adverse event	Experience of adverse effect; stopping the medication after experience the side effect, who is the first consultant
HR-QOL*	Health related quality was measured by using modified McGill and EQ-5D

* HR-QOL were re-evaluated during June-July 2008

3.8.1.1.3 Adaptation and translation of questionnaire

The questionnaires used to measure HR-QOL were derived from two widely used questionnaires which are McGill quality of life questionnaire and EQ-5D (VAS). The EQ-5D (VAS) was used in the original Thai version without any changes. However, McGill quality of life questionnaire was translated and modified to match the context of the patients in the study site (Box Annex-1).

Box 3-1: Method of translation and modification of the McGill quality of life questionnaire

Method of translation of McGill Questionnaire
Two Thai medical doctors including the researcher independently translated the original McGill questionnaire from English to Thai in a way that the patients could easily understand and answer. Three medical and one public health officers reviewed the translations. Then, the questionnaire was back-translated form Thai to English again. The original and back-translated questionnaire were compared and revised by the medical and public health officers together with the researcher as well as the PLHA.

Modification of the McGill Questionnaire
Like the original McGill questionnaire, participants were asked to report their quality of life within the last 2 days. However, there were some modifications which were the result from piloting the questionnaire (see section below). The modification were

1. One question was added which asked the participants to compare overall quality of life in the past 2 day to just before entering the government ART programme.
2. Scale was reduced from 11 scales (0-10) to 5 scales (0-4) which is more convenient and more understandable for Thai context
3. There was short description for every scale in each question e.g. "Level I" (1) means "Very bad" and "Level V" (5) means "Excellent"
4. The questionnaire was magnified at 2 questions per page including the 0-4 scales; this was used during the interviews. It allowed respondents to read ,visualize and point out the scale which suit their health status for more accurate answer

3.8.1.1.4 Improving reliability and validity of the questionnaire

For a survey, construction of the questionnaire is one of the important issues. To develop a tool to measure the five areas of interest, related literatures search was performed. The contents of the questionnaire were constructed by the researcher together with people who living with HIV/AIDS to improve the validity of the questionnaire. Multiple-item scales were applied in the questionnaire wherever possible to enhance reliability of the participants' given results. Criterion validity of the study has been improved by using mfti-measures to reveal the effectiveness of the programme. Then, the first draft was produced

Ambiguous questions were avoided, as were statements that included more than one issue. Statements were kept short and language simple. Participants would be asked to respond to individual statements and allow the interviewers to circle the chosen choices. The second draft of the questionnaire was reviewed for face validity with five patients of various ages from 3 hospitals. Difficult questions were reworded and ambiguous questions excluded. Some relevant questions were also added. The third draft was reorder. Non-randomized, convenience sample of 30 patients were requested to complete the questionnaire on the

purpose of pilot study wording and coding in the questionnaire was carefully checked again. However, the results were only tested for internal consistency which involved testing for homogeneity of the results (inner-item correlations and Cronbach's alpha) due to the single administration of the questionnaire.

3.8.1.1.5 Pilot study of the questionnaire used for the survey

The pilot study was conducted in Mae-On district which is 25 kilometre away from Chiang Mai province to check for the completeness of the questionnaire. The questionnaire was piloted with 30 PLHA who were currently being treated with antiretroviral drug under the programme at one district hospital. Two leaders of PLHA from hospital in that district were trained, using the steps of training mentioned above, to use the questionnaire. The piloting took 2 weeks to complete the interviews. Problems related to word in questions, frame of reference, description in the questionnaire occurred during the pilot study were recorded discussed between the trained interviewers and the researchers. Information from 30 respondents was tested for validity (face, content, construct) and reliability (internal consistency using Cronbach's alpha). The questionnaires were, then, revised and modified. Some questions were omitted and added. Order of questions was re-arranged. Words were clarified and simplified to use among PLHA. After piloting, the final version of questionnaire was produced and was used to determine effectiveness.

3.8.1.2 Treatment outcome

The treatment outcomes of the present study of the both prospective and retrospective cohorts consists four main measures including survival of the participants, health-related quality of life, immunological improvement of the CD4 cell count and duration on the first-line regimen. Their definitions as well as sources of information were shown in Table 3-4.

Table 3-4: Treatment outcomes of 302 participants

Treatment outcome	Definition	Source of information*
Survival	All-cause mortality occurring during the follow-up period were executed on a continuous basis from physician reports and through record linkages carried out with ICD 10 (international classification of the disease version 10) death classification	▪ Patient medical record ▪ Contact related facilities where patients referred to ▪ Contact with patient family
Health-related quality of life	Changes in health-related quality of life measured using modified McGill questionnaire and EQ-5D	Interviewed using the questionnaires
Immunological response	CD4 cell counts approached the level of 200 and 500 cell/uL	▪ Patient medical record ▪ Contact related facilities where patients referred to ▪ Contact with patient family
Duration on 1st line regimen	Duration on 1st line regimen before changing regimen and reason for changes	▪ Patient medical record ▪ Contact related facilities where patients referred to ▪ Contact with patient family

* For those who might die or be referred to other hospitals as well as patients who terminates due to other causes, their outcome were sought through medical record, contact to related facilities (if they were referred out) and contact (both directly and indirectly) with their families.

The survival is the key outcome measure for success of the treatment as the HIV/AIDS is considered as a fatal disease. It was also measured as the researcher aimed to compare the success rates of the treatment in developed and developing countries. In the present study, all-cause mortality of the participants was used as an outcome measure.

As the treatment has turned the disease into a chronic manageable disease, quality of life data have added useful information to treatment trials which sometimes supports the findings of the trials (Bozzette, Kanouse et al. 1995); (Revicki, Moyle et al. 1999); (Nieuwkerk, Gisolf et al. 2000), and sometimes contradicts trial outcomes (Safrin, Finkelstein et al. 1996) emphasising the importance of obtaining information of adverse effects and tolerability rather than just survival. Moreover, studies regarding quality of life in PLHA being treated with HAART are still limited in developing countries.

Health-related quality of life (HR-QOL); The widely used measurement of HR-QOL for HIV-infected individuals can be classified into 2 groups; generic measures , such as SF-36

(Arpinelli, Visona et al. 2000); (Garcia Ordonez, Mansilla Francisco et al. 2001); (Wu, Jacobson et al. 2002) and Euroqol (EQ-5D) (Wu, Jacobson et al. 2002); (Ichikawa and Natpratan 2004), and HIV specific measures, such as MOS-HI (Ichikawa and Natpratan 2004) . However, there is no consensus regarding the best measurement approach.

In the present study, two approaches were used to measure HR-QOL, which are (i) EQ-5D Thai version and (ii) Modified McGill Quality of Life Questionnaire. The former questionnaire was used as it is simple, easy to use and available in Thai version. However, in each domain of the EQ-5D, only three possible choices can be answered. To add more information regarding quality of life, another measure was used. At the beginning, the researcher aimed to use the specific measure like MOS-HIV. However, at it was still underdevelopment at the time the study conducted in 2004. Thus, the researcher had to search for another general quality of life measure which adds more information rather than five domains in the EQ-5D. At that time, McGill Questionnaire was chosen as some domains such as existential feeling and support are interesting and might allow us to have an insight about quality of life of HIV/AIDS patients

This subgroup of the prospective cohort was randomly drawn from the list of those who managed to survive and who was interviewed during the survey (May-July 2004). This follow up study of 97 participants was conducted during June-July 2007 to identify the changes of HR-QOL after the period of three years on ART. However, in this subgroup, the sample size was not calculated as the research aimed only to have some information regarding quality of life of the patients

For immunological improvement, CD4 cell count, which is the surrogate marker for initiating and monitoring the treatment was also measured. As we know that at patient with CD4 cell count lower than 200 cell/uL of CD4 cell count is at risk of developing opportunistic infection and at the level of 500 cell/uL was associated with AIDS free

duration (Kawado, Hashimoto et al. 2006). Thus, the two cut points were used as the outcomes measures in this present study. For the duration on the first-line regimen, this aims to identify the ability of the care provider in term of adverse effect and choice of regimen used as well as the chance to develop drug resistance of the patients.

3.8.2 Retrospective cohort

On May 1, 2007, similar treatment outcomes as those used in prospective cohort of 199 participants were assessed (see section 3.8.1.2). However, their baselines which also gathered in the prospective cohort had to be sought regarding

i. Age
ii. Gender
iii. Socioeconomic status
iv. Education
v. Health insurance
vi. Accessibility to the hospital
vii. Being member of PLHA self-help group
viii. Being naïve to the ART
ix. Baseline CD4 cell counts
x. Disease staging before starting ART (according to WHO classification)
xi. Initial prescribed regimen

At the time of initiation of the treatment were attempted to identify through medical record, contact to related facilities (in case they were referred out) and contact (both directly and indirectly) with their families by the researcher and trained interviewers. However, as this part was done retrospectively, the chance of missing data was also higher. However, the information at the baseline and outcome were sought and verified for accuracy as much as possible with the constraints imposed by the retrospective cohort nature.

3.8.3 Quality assurance for the interview

As the interviews were one of the important methods in the present study to retrieve information during the survey, evaluation of HR-QOL and identification of baseline characteristics of the patients in retrospective cohort, to avoid bias of the interviewers being overly optimistic about the programme, the following processes were conducted.

1. All interviewers were trained carefully to ensure the validity of information. The purposes and objectives of the study were informed. Possible bias was documented and interviewers were asked to avoid these.
2. Every interviewer was required to read every single question and choice in the questionnaire. Testing for their understanding was performed, at the end of each question, the meaning of the question and choice was informed after discussion.
3. The researcher was at the interview room together with the interviewer team. Any inquiries would be solved by the team together. In case where the researcher was not available, other interviewers can consult via the mobile phone at all time
4. During the interview, the interviewers read every single question for the patients. Answers were record directly onto questionnaire. The questions and their scales were magnified and were given to the patients. The patients were informed about the scale instructions. Then, they were asked to choose the scale that suited their health status the most. This allowed the patient getting along with the questions
5. At the end of each day after finishing all of the interviews sessions, the interviewers discussed and validated the given information. If there were any enquiries, the interviewer team, then, would arrange to talk with the respondent again to rectify any possible mistakes

3.8.4 Data testing and cleaning

Before proceeding with the analysis, all data both from the medical record and from the patient interview were entered using double entry verification and were tested for logical consistency set up in the coding specification and were checked for wide codes by generating a frequency distribution for each variable by the researcher. Any missing data was where possible validated with the staff at the hospital by comparing to the original copy of patient visit form and the patient's OPD card.

3.8.5 Data Analysis

Data were analysed using SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA). For the treatment outcomes like survival, the immunological improvement and duration on the first-line regimen, the survival and time to event analysis were used. For the survival analysis, all patients were taken into account. Cumulative incidences of the outcomes were estimated using Kaplan-Meier methods.

To compare the contribution of the investigated variables to the outcomes, survival and time to event function were compared between groups using the log-rank test. Cox proportional hazards regression was used to compute single variable and adjusted relative hazards and 95% confidence interval (CI). The time since the initiation was measured in weeks. The assumption of proportional hazards was validated by the inspection of log (-log (survival function)) estimates against log time plots. Participants who were still alive at the end of the study period were considered as right censored as of May 1, 2007. The proportional hazard models were adjusted for all variables that were significant in single variable Cox model. Variables considered to have influence on survival are show in the Table 3-5. Repeated analyses for other treatment outcomes (see 3.7.1.2 for treatment outcomes) were done similarly with the survival.

Variables from the participants characteristic and effectiveness were analysed using methods of descriptive to summarize and describe the variables, and inferential statistics to describe to infer and predict outcomes of the study. The Chi-square statistic (χ^2) was used to test for associations between categorical variables (Fisher's exact test was used if appropriate). The ANOVA test was also used to test for differences among continuous variables. All tests were two-tailed, with a statistical significance level of $P < 0{\cdot}05$.

Table 3-5: Baseline characteristics of the participants that might affect the outcomes

Potential confounder	Measure
Gender	Initial interview and medical record
Age	Initial interview and medical record
Socio-economics	
Main occupation	Structured set of questions in interview to assess
Being main wage earner	household income (questions 5 to 7 in the interview
Monthly income	schedule given in Annex 4 6.4.5)
Monthly household income	
Education	Initial interview
Health scheme	Initial interview and medical record
Distance between the hospitals and their houses	Initial interview
Being member of PLHA self-help group	Initial interview
Being naïve to the ART	Initial interview and medical record
Baseline CD4 cell counts	Medical record
Baseline WHO stage IV	Medical record
Initially prescribed with PI-based regimen	Medical record
Type of ARV clinic	Staff interview

*see Chapter 2 for literatures regarding factors that might influence the treatment outcome

This chapter has summarised the methodology employed to evaluate the null hypothesis that socioeconomic status was irrelevant in determining outcome of patients enrolled into the National ART programme in Thailand. Chapter 4 progresses to analyse the results obtained using this methodology to ascertain factors that were identified as being significant in determining outcomes generated by the programme.

Table 3-6: Plan of data analysis

Questions	Data	Statistics used
Are there any differences in relation to baseline characteristics between death and non death patients?	Baseline characteristic including age, gender, education, type of health insurance, member of PLHA self-health group, occupation, average income, average household income, type of accommodation, distance and duration to get to the hospital, base line CD4 cell counts, WHO classification, baseline body weight, duration of HIV infection, duration of ART, regimen, naïve to ART, adverse reaction, type of health facilities, self reported adherence, HR-QOL	Baseline characteristics cross tab with status as death and non death, Chi-square test for category variable and t-test for continuous variable (crude RR). Later, all significant variables were put in the logistic regression model to identify group of variable that predicts the death (adjusted RR)
Is there any association between age (and other confounders) and survival?	Age and other confounders including gender, socioeconomic, baseline CD4 cell counts, self reported adherence, type of health facilities, support from the PLHA self-help group, regimen of ART, naïve to the treatment, duration and distance between home and hospital, WHO classification	Cumulative mortality rates were estimated using Kaplan-Meier methods. Survival curves were compared between groups (regarding the confounders) with the log-rank test
What is the model to predict the survival?	Baseline characteristic in relation to age, gender, education, type of health insurance, member of PLHA self-health group, occupation, average income, average household income, type of accommodation, distance and duration to get to the hospital, baseline CD4 cell counts, WHO classification, baseline body weight, duration of HIV infection, duration of ART, regimen, naïve to ART, adverse reaction, type of health facilities, self reported adherence, HR-QOL	Regression to identify associated factor using Cox proportional hazard model

CHAPTER 4
RESULTS

4 Results

In this chapter, the results of the present study are shown regarding the main objectives and outcomes of ART (see section 3.2). These sections were:-

1. Outcomes of the ART in relation to survival of 501 cases, health-related quality of life in the subgroup of 97 participants during the period of 3 years (between 2004 and 2007), improvement of the CD4 cell count and duration on the first-line regimen.
2. Investigation of the factors that might influence the ART outcomes
3. Survey of ART programme in Chiang Mai, Northern Thailand to identify the patient and health care provider characteristics;

4.1 Outcomes of the antiretroviral therapy

A total of 501 cases were initiated on ART between March 1 2001 and April 30 2004. This also included 73 cases who started the treatment slightly earlier than that date. The outcomes on treatment were assessed on May 1 2007; 139 from doctor-led ARV clinic, 251 from large nurse-led clinic and 111 from small nurse-led clinic. Of these participants, 28 were lost to follow up. At the baseline, 56% were women (see Table 4-1), the average age was 36, most were general labourers (61.0%), and 57% were the main wage earner in their families.

Table 4-1: Baseline characteristics of 501 participants

Characteristics	N=501
Mean age: Year (SD)	36.0 (18.3-60.5)
Gender	
Male	217 (43.4)
Female	283 (56.6)
Main Occupation: N (%)	
Unemployed	70 (15.2)
Farmer or gardener	26 (5.6)
Self employed	57 (12.3)
General Labourer	282 (61.0)
Housewife	25 (5.4)
Other	2 (0.4)
Being main wage earner: N (%)	277 (57.9)
Median monthly income: 1,000 THB (IQR)	3.0 (2.0-4.5)
Median monthly household income: 1,000 THB (IQR)	4.5 (3.0-7.0)
Education: N (%)	
No formal educational	126 (26.6)
Primary school	214 (45.1)
Secondary school	105 (22.1)
Higher than secondary school	29 (6.2)
Health insurance: N (%)	
Civil servant medical benefit scheme	20 (4.1)
Fee for service	15 (3.0)
Social security scheme	43 (8.8)
Universal coverage	409 (84.0)
Being member of people who living with HIV/AIDS self-help group: N (%)	252 (53.8)

SD= standard deviation; IQR=inter-quartile range

Table 4-2: Clinical information of 501 participants

Clinical information	N=501
Previously treated with antiretroviral therapy: N (%)	123 (26.5)
Median time between HIV diagnosis and initiation of the treatment: Year (IQR)	5.0 (2.0-8.0)
Years on antiretroviral treatment: N (%)	
2.0-4.0 years	276 (61.9)
4.1-6.0 years	142 (28.9)
6.1 or more	73 (14.9)
Median (IQR)	3.7 (3.5-4.9)
WHO staging before treated: N (%)	
Stage II	50 (10.6)
Stage III	98 (20.8)
Stage IV	324 (68.6)
Present WHO staging: N (%)	
Stage II	45 (11.4)
Stage III	81 (20.5)
Stage IV	269 (68.1)
Median baseline CD4 cell counts: cell/μL (IQR)	61 (18-173)
Initial regimen: N (%)	
GPO-VIR (3TC+d4T+NVP)	355 (81.8)
AZT+3TC +SQV+RTV	23 (5.3)
D4T+3TC+EFV	20 (4.6)
AZT+DDI+NVP	19 (4.4)
AZT+3TC+EFV	17 (3.9)
Latest regimen: N (%)	
GPO-VIR (3TC+d4T+NVP)	229 (66.0)
GPOZ (AZT+d4T+NVP)	72 (20.7)
AZT+3TC+EFV	17 (4.9)
EFV+IDV+RTV	16 (4.6)
AZT+3TC +SQV+RTV	13 (3.7)

SD=standard deviation; IQR=inter-quartile range; NA=not applicable; GPO=Government Pharmaceutical Organisation; AZT=Zidovudine; d4T=Stavudine; 3TC=Lamivudine; NVP=Nevirapine; EFV=Efavirenz; IDV=Indinavir; RTV=Ritonavir; SQV=Saquinavir

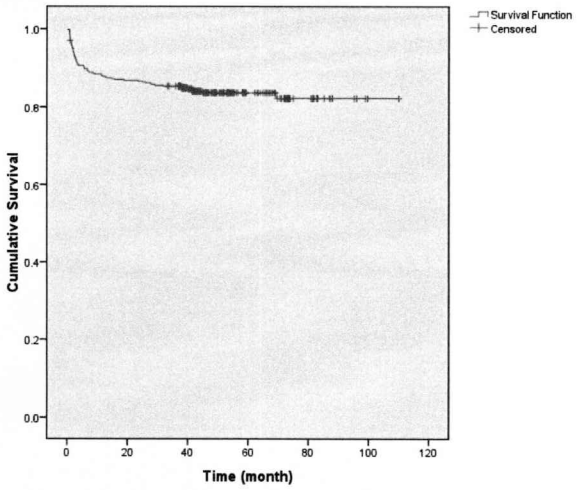
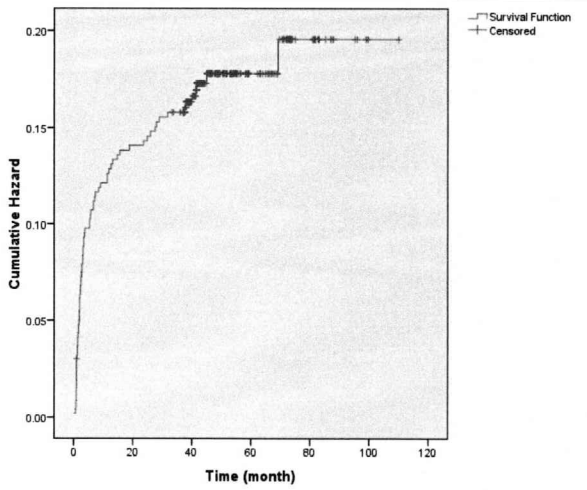
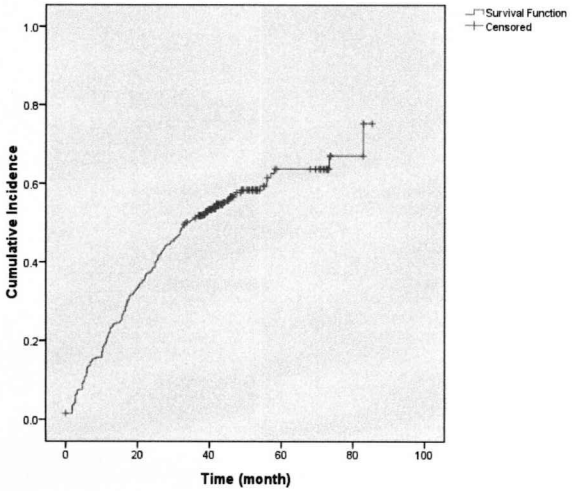
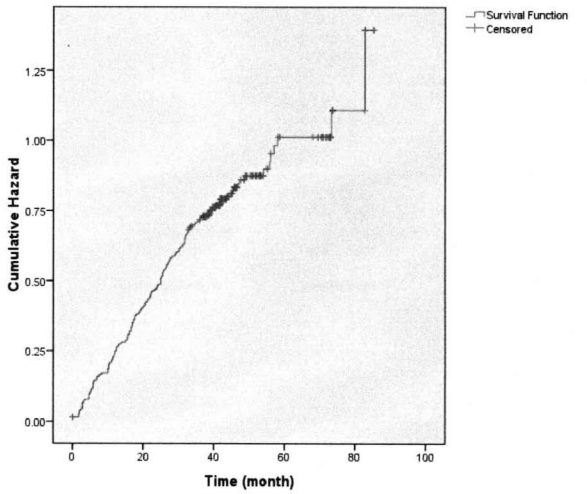
In relation to clinical information, three quarters of them were naïve to ART, with the median time since initiation of ART in the national programme being 3.7 years (see Table 4-2). At initiation, nearly 90% of the patients were in an advanced stage (either in WHO Stage III or IV) with initial CD4 cell counts being low (median= 61 cell/uL). Most patients (70%) were started with the first-line regimen recommended by the national ART programme (GPO-Vir). More than half remained on this regimen by May 2007. Despite the fact that GPO-Vir was the recommended first-line regimen in the programme, not all patients received this regimen due to (i) the drug becoming recommended in 2003, but participants had been treated since 2001 and (ii) before prescribing this regimen, participants were tested for tolerability and side effects.

In this study, the effects of ART on survival was analysed in detail using information regarding all participants who started treatment between May 2001 and May 2004. The treatment outcomes of this study were analysed as at May 2007. With a median follow up period of 3.7 (IQR=3.6-4.9) years, 76 patients died, 13 cases had disease progression leading to a change in the WHO staging (see Table 4-3) and 31% had to change prescribed ART regimens from their initial therapy. Five cases had decided to terminate the treatment themselves, eight cases were lost to follow up and seventy-five cases were transferred to nearby health facilities (information regarding treatment outcomes of those who transferred to other hospitals was obtained from their new health facilities). More than half CD4 cell counts approached 200 cell/uL and a quarter of them approached 500 cell/uL. Approximately 20% of patients experienced adverse reaction from using ART with 20 of them being resistant to the prescribed treatment. Table 4-4 provides details of four treatment outcomes including mortality, CD4 cell counts of 200 and 500 cell/uL and changing of prescribed regimen and were analysed through a hazard function and either survival or time to event density function.

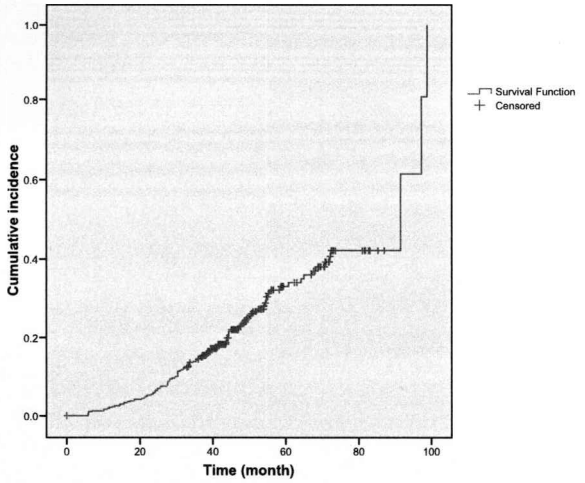
Table 4-3: Treatment outcomes

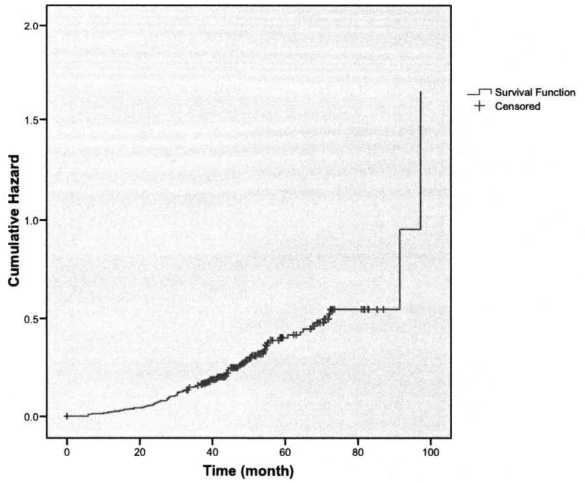
Treatment outcomes	N (%)
Death	76 (16.0)
CD4 cell counts	
More than 200 cell/μL	271 (54.2)
More than 500 cell/μL	121 (24.2)
Changing of treatment regimens	157 (31.3)
Adverse event	93 (18.6)
Drug resistance	24 (4.8)
Advance staging	13 (2.6)
Self-decided to termination of antiretroviral therapy	5 (1.0)
Lost to follow up	28 (5.6)
Referring out to other hospitals	75 (15.0)

Table 4-4: Survival function/time to event and hazard function of four treatment outcomes

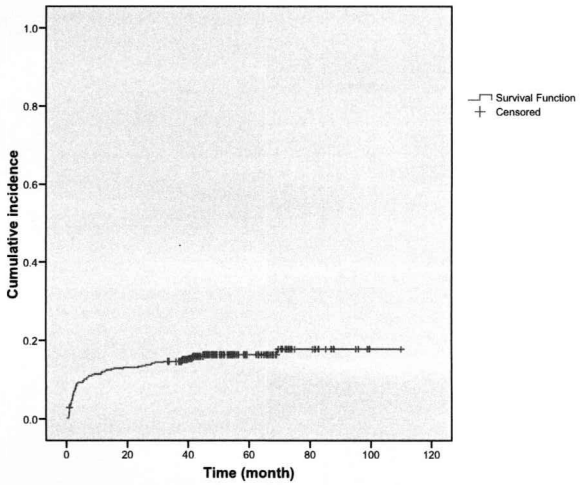
Treatment outcome	Survival function/time to event function	Hazard function
Mortality		
Event of having CD4 cell counts approach the level of 200 cell/μL		

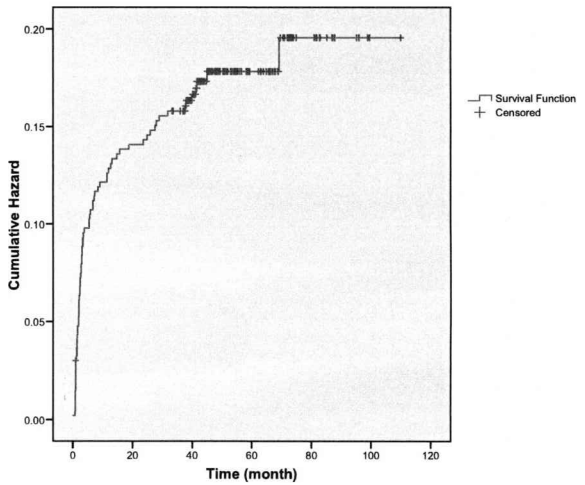
Event of having CD4 cell counts approach the level of 500 cell/μL





Event of changing ART regimen





4.1.1 Mortality

In relation to all-cause mortality, 76 patients died during the period of analysis. These included two cases that committed suicide (hanging and poison drinking) and one case from a motorcycle accident. In these 76 cases, their average age was 36 years old and 60% of them were male. 56% of deaths occurred in the large nurse-led clinic; 32% in the small-nurse-led clinics and 12% in the doctor-led clinic. Nearly all patients who died were in the universal health scheme but only half of them were members of the PLHA self-help group. From a clinical perspective, generally they were in WHO stage IV with very low baseline CD4 with a median of 18 cell/uL. In relation to ART, GPO-Vir (d4T+3TC+NVP) was the regimen initially prescribed to 70% of patients who subsequently died. The mean survival time was 93.1 months (SD=1.8), however, as less than 50% of the participants died during the period of analysis, thus, no median survival time could be determined (see Table 4-4)

4.1.2 Health-related quality of life

4.1.2.1 Health related quality of life in 302 participants in 2004

In this study, two sets of questionnaire were used to determine patient's aspect of health-related quality of life; modified McGill's questionnaire and EQ-5D (Thai version). They were used to measure the impact of the government ART programme on the patient's emotional, social and physical wellbeing. Questions related adverse effects of the ART, stigma, sexual behaviour and questions which asked the participants to directly compare health status before and after ART were presented in section 4.3.7 - section 4.3.9.

Table 4-5: HR-QOL using Modified McGill questionnaire-single question

Modified McGill Questionnaire, Single question	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
Quality of life in the past 2 days				
Level I (Very bad)	5 (5.0)	2 (1.6)	2 (2.5)	9 (3.0)
Level II	16 (16.0)	11 (9.0)	11 (13.8)	38 (12.6)
Level III	51 (51.0)	71 (58.2)	39 (48.8)	161 (53.3)
Level IV	23 (23.0)	33 (27.0)	21 (26.3)	77 (25.5)
Level V (Excellent)	5 (5.0)	5 (4.1)	7 (8.8)	17 (5.6)
Quality of life in the past 2 days comparing to before entering the governmental antiretroviral treatment programme				
Level I (Extremely worse)	0	0	0	0
Level II	0	2 (1.6)	3 (3.8)	5 (5.7)
Level III	23 (23.0)	13 (10.7)	10 (12.5)	46 (15.2)
Level IV	61 (61.0)	89 (73.0)	47 (58.8)	197 (65.2)
Level V (Extremely better)	16 (16.0)	18 (14.8)	20 (25.0)	54 (17.9)

For the modified McGill's questionnaire, the participants were asked to answer each question with the range of Level I to Level V. They were given the meaning of the 2 extremes (Level I and Level V). For instance, Level I means extremely bad while Level V means extremely good. Then, the participants were asked to choose either Level I, II, III, IV or V that match them the most for each questions. The questions consist of two single-item scale (SIS) questions and 16 sub-measure questions. The first two SIS questions were used to ask the participant for overall quality of life in the past 2 days and in the past 2 days comparing to just before starting the ART. The other 16 questions were used to measure HR-QOL in sub-dimensions.

From the first SIS question which asked participants to document their health status in the previous 2 days, about half of the 302 participants documented their health in the past at level of 2 (fair health status) (see Table 4-5). For the second SIS question which asked participants to compare their quality of life in the past 2 days and the just before entering the programme, about 80% reported of better health after taking the ART. However, there were 5 cases (1.7%) reported of worse health status comparing to before taking the ART. In these 5 participants, 2 of them used to experience minor adverse effects from the ART and 1 of them had severe side effects and stopped taking the medicine. Four of them also showed good compliance to the medicine.

In relation to the sub-measures including the evaluation of physical well being, psychological status, existential feeling and supports given, the findings were shown in Table 4-6 till Table 4-9. The level of HR-QOL of the participant were similar across the 3 clinics

Table 4-6: Physical well being using modified McGill questionnaire

Physical well being in the past 2 days...	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
I have felt that my physical is				
Level I (extremely weak)	2 (2.0)	0	0	2
Level II	9 (9.1)	3 (2.5)	3 (3.8)	15 (5.0)
Level III	28 (28.3)	38 (31.1)	28 (35.0)	94 (31.2)
Level IV	55 (55.6)	71 (58.2)	46 (57.5)	172 (57.1)
Level V (very well)	5 (5.1)	10 (8.2)	3 (3.8)	18 (6.0)

Table 4-7: Psychological status using modified McGill questionnaire

Psychological status in the past 2 days	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
I have been depressed				
Level I (not at all)	61 (61.6)	97 (79.5)	62 (77.5)	220 (73.1)
Level II	30 (30.3)	17 (13.9)	14 (17.5)	61 (20.3)
Level III	5 (5.1)	5 (4.1)	3 (3.8)	13 (4.3)
Level IV	3 (3.0)	3 (2.5)	1 (1.3)	7 (2.3)
Level V (extremely)	61 (61.6)	97 (79.5)	62 (77.5)	220 (73.1)
I have been nervous or worried				
Level I (not at all)	58 (58.6)	88 (72.1)	52 (65.0)	198 (65.8)
Level II	21 (21.2)	20 (16.4)	18 (22.5)	59 (19.6)
Level III	13 (13.1)	5 (4.1)	2 (2.5)	20 (18.0)
Level IV	5 (5.1)	7 (5.7)	6 (7.5)	18 (6.0)
Level V (extremely)	2 (2.0)	2 (1.6)	2 (2.5)	6 (2.0)
How much of the time did you feel sad				
Level I (never)	54 (54.5)	67 (54.9)	49 (61.3)	170 (56.5)
Level II	35 (35.4)	47 (38.5)	25 (31.3)	107 (35.5)
Level III	3 (3.0)	4 (3.3)	4 (5.0)	11 (3.7)
Level IV	6 (6.1)	4 (3.3)	1 (1.3)	11 (3.7)
Level V (always)	1 (1.0)	0 (0.0)	1 (1.3)	2 (0.7)
When I thought of the future, I was				
Level I (not afraid)	39 (39.4)	63 (51.6)	33 (41.3)	135 (44.9)
Level II	30 (30.3)	30 (24.6)	29 (36.3)	89 (29.6)
Level III	20 (20.2)	16 (13.1)	13 (16.3)	49 (16.3)
Level IV	7 (7.1)	6 (4.9)	2 (2.5)	15 (5.0)
Level V (terrified)	3 (3.0)	7 (5.7)	3 (3.8)	13 (4.3)

Table 4-8: Existential feeling using modified McGill questionnaire

Existential feeling in the past 2 days	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
My life has been				
Level I (utterly meaningless and without purpose)	2 (2.0)	3 (2.5)	2 (2.5)	7 (2.3)
Level II	14 (14.1)	16 (13.1)	12 (15.0)	42 (14.0)
Level III	39 (39.4)	54 (44.3)	29 (36.3)	122 (40.5)
Level IV	29 (29.3)	33 (27.0)	26 (32.5)	88 (29.2)
Level V (purposeful and meaningful)	15 (15.2)	16 (13.1)	11 (13.8)	42 (14.0)
When I thought about my whole life, I felt that in achieving life goals I have				
Level I (made no progress whatsoever)	15 (15.2)	20 (16.4)	8 (10.0)	43 (14.3)
Level II	32 (32.3)	42 (34.4)	26 (32.5)	100 (33.2)
Level III	33 (33.3)	40 (32.8)	36 (45.0)	109 (36.2)
Level IV	12 (21.1)	13 (10.7)	8 (10.0)	33 (11.0)
Level V (progressed to complete fulfilment)	7 (7.1)	7 (5.7)	2 (2.5)	16 (5.3)
When I thought about my life, I felt that my life to this point has been				
Level I (completely worthless)	6 (6.1)	1 (0.8)	1 (1.3)	8 (2.7)
Level II	16 (16.2)	12 (9.8)	6 (7.5)	34 (11.3)
Level III	53 (53.5)	83 (68.0)	45 (56.3)	181 (60.1)
Level IV	18 (18.2)	16 (13.1)	22 (27.5)	56 (18.6)
Level V (very worthwhile)	6 (6.1)	10 (8.2)	6 (7.5)	22(7.3)
I have felt that I have				
Level I (no control over my life)	0	1 (0.8)	0 (0.0)	1 (0.3)
Level II	15 (15.2)	5 (4.1)	11 (13.8)	31 (10.3)
Level III	52 (52.5)	72 (59.0)	36 (45.0)	160 (53.2)
Level IV	28 (28.3)	31 (25.4)	29 (36.3)	88 (29.2)
Level V (completely control over my life)	4 (4.0)	13 (10.7)	4 (5.0)	21 (7.0)
I felt good about myself as a person				
Level I (completely disagree)	5 (5.1)	5 (4.1)	1 (1.3)	11 (3.7)
Level II	60 (60.6)	73 (59.8)	46 (57.5)	179 (59.5)
Level III	27 (27.3)	33 (27.0)	23 (28.8)	83 (27.6)
Level IV	7 (7.1)	11 (9.0)	10 (12.5)	28 (9.3)
Level V (complete agree)				
The past 2 days were				
Level I (burden)	1 (1.0)	0	2 (2.5)	3 (1.0)
Level II	14 (14.1)	12 (9.8)	6 (7.5)	32 (10.6)
Level III	64 (64.6)	82 (67.2)	60 (75.0)	206 (68.4)
Level IV	16 (16.2)	23 (18.9)	10 (12.5)	49 (16.3)
Level V (a gift)	4 (4.0)	5 (4.1)	2 (2.5)	11 (3.7)

Table 4-9: Evaluation of support using modified McGill questionnaire

Support in the past 2 days	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
The world has been				
Level I (an impersonal unfeeling place)	0	0	1 (1.3)	1 (0.3)
Level II	0	3 (2.5)	2 (2.5)	5 (1.7)
Level III	73 (73.7)	76 (62.3)	58 (72.5)	207 (68.8)
Level IV	18 (18.2)	32 (26.2)	14 (17.5)	64 (21.3)
Level V (caring and responsive to my needs)	8 (8.1)	11 (9.0)	5 (6.3)	24 (8.0)
I have felt supported				
Level I (not at all)	40 (40.4)	15 (12.3)	21 (26.3)	76 (25.2)
Level II	18 (18.2)	30 (24.6)	20 (25.0)	68 (22.6)
Level III	24 (24.2)	61 (50.0)	27 (33.8)	112 (37.2)
Level IV	11 (11.1)	13 (10.7)	9 (11.9)	33 (11.0)
Level V (completely)	6 (6.1)	3 (2.5)	3 (3.8)	12 (4.0)

In relation to EQ-5D, nearly all participants stated their health status as no problem or with minor problem in 5 dimensions of EQ-5D (see Table 4-10). For the EQ-5D (VAS) participants were requested to mark their health status on the date of the interviews directly onto the provided scale. Additionally, with the scale 0-100 of the EQ-5D visual analogue scale (VAS), the mean score was 79 with only 1 case marked the score at 0. The rest of the participants marked the score at 30 or above (see Table 4-10). This showed the overstated of health status when using EQ-5D (VAS), thus, using this tool to measure health-related quality of life warrants careful interpretation in Thai culture.

Table 4-10: HR-QOL using EQ-5D

EQ-5D	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total
Mobility				
I have no problems in walking about	89 (89.0)	115 (94.3)	57 (71.3)	261 (86.4)
I have some problems in walking about	10 (10.0)	7 (5.7)	23 (28.8)	40 (13.2)
I am confined to bed	1 (1.0)	0	0	1 (1)
Self-Care				
I have no problems with self-care	98 (98.0)	121 (99.2)	78 (97.5)	297 (98.3)
I have some problems washing or dressing myself	1 (1.0)	1 (0.8)	2 (2.5)	4 (1.3)
I am unable to wash or dress myself	1 (1.0)	0	0	1 (0.3)
Usual activities				
I have no problems with performing my usual activities	92 (92)	118 (96.7)	72 (90.0)	282
I have some problems with performing my usual activities	6 (6.0)	4 (3.3)	7 (8.8)	17 (5.6)
I am unable to perform my usual activities	2 (2.0)	0	1 (1.3)	3 (1.0)
Pain/Discomfort				
I have no pain or discomfort	64 (64.0)	94 (77.0)	52 (65.0)	210 (69.5)
I have moderate pain or discomfort	36 (36.0)	28 (23.0)	28 (35.0)	92 (30.5)
I have extreme pain or discomfort	0	0	0	0
Anxiety/Depression				
I am not anxious or depressed	56 (56.0)	99 (81.1)	59 (73.8)	214 (70.9)
I am moderately anxious or depressed	43 (43.0)	23 (18.9)	19 (23.8)	85 (28.1)
I am extremely anxious or depressed	1 (1)	0	2 (2.6)	3 (1.0)
Visual Analogue Scale (VAS)				
Mean (standard deviation)	76.9 (17.6)	80.9 (12.1)	78.5 (18.0)	79.0 (15.8)
Range	40.0-100.0	40.0-100.0	0.0-100.0	0.0-100.0

With multi-question used to document HR-QOL, their correspondences were tested. It was found that there were a strong correlation regarding modified McGill questionnaire (2 SIS questions and 5 sub-measures) and the EQ-5D (VAS) with Pearson correlation, $p< 0.01$. (Table 4-11).

Table 4-11: Correlation between health-related quality of life measures

Correlation	Physical symptom	Physical well-being	Psychological	Existential	Support	SIS-1	SIS-2	EQ-5D (VAS)
Total	0.53**	0.70**	0.63**	0.67**	0.60**	0.52**	0.29**	0.48**
Physical symptom	-	0.42**	0.27**	0.11	0.01	0.13*	0.07	0.25**
Physical well-being	-	-	0.27**	0.31**	0.15**	0.37**	0.25**	0.38**
Psychological	-	-	-	0.21**	0.18**	0.37**	0.11	0.33**
Existential	-	-	-	-	0.49**	0.46**	0.32**	0.26**
Support	-	-	-	-	-	0.28**	0.14*	0.27**
SIS-1	-	-	-	-	-	-	0.26**	0.30**
SIS-2	-	-	-	-	-	-	-	0.19**

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

4.1.2.2 Health-related quality of life of a subgroup of 97 participants in 2004 and 2007

In this study, a group of 97 participants who were alive in 2007 and had been interviewed in 2004 were randomly selected to assess the impact of their treatment on their health-related quality of life. A simple randomization technique was used, allocating identification numbers randomly to participants. They were later interviewed to identify the impact of ART on HR-QOL during the three years of their treatment (2004-2007) together with characteristics which may explain any changes in the 97 participants. HR-QOL results in 2004 were not a true baseline (before initiation of HAART), but consisted of patients who had already experienced a variable amount of treatment time on ART. As such, the length of time individuals had been on ART in 2004 was a major factor influencing treatment outcomes in relation to HR-QOL. During initiation of ART in the early stage, HR-QOL will improve significantly prior to reaching a plateau and stabilizing. In 2004, the median interval time between initiation of ART and interview was 7.7 months (IQR=5.8-14.7), thus, some participants may already have improved HR-QOL and might express no change in HR-QOL at the reassessment three years later.

Of the 97 participants, 28 came from the doctor-led ARV clinic in provincial hospital, 38 from the large nurse-led clinics and 31 from the small nurse-led clinic from the two district hospitals, with 32% of participants being men, and 68% women (see Table 4-12). The average age was 38 years for both men and women at the time of interview in 2004 with the majority of participants (70%) having either no formal education or simply having completed primary education. The mean length of time since they became aware of their HIV status was about ten years and nearly 90% of them were prescribed with first line regimen (GPO-Vir; locally-produced cocktail regimen of 3TC+d4T+NVP). In all characteristics, this sub-group were not significantly different from the group of 302 participants from which they were drawn in relation to age, gender, education, health insurance and prescribed medication. Comparing with the subgroup of 97 participants and a

total 0f 302 who were interviewed in 2004, it found that their characteristics were quite similar, the only difference was that the number of participants

Table 4-12: Baseline characteristics of the subgroup of 97 participants comparing that of 302 participants from the survey in 2004

Baseline characteristics	N=97	N=302
Mean age: Years (SD)	37.9 (6.7)	37.1 (7.1)
Gender: N (%)		
Male	31 (32)	119 (39.4)
Female	66 (68)	183 (60.6)
Education: N (%)		
No formal educational	28 (28.9)	82 (27.2)
Primary school	53 (54.6)	164 (54.3)
Secondary school	13 (13.4)	36 (11.9)
Higher than secondary school	3 (3.1)	20 (6.6)
Marital status: N (%)		
Single	12 (12.4)	43 (14.3)
Married or living with partner	38 (39.2)	119 (39.7)
Separated/Divorce	8 (8.3)	30 (10.0)
Widow/ widower	39 (40.2)	108 (36.0)
Type of health insurance: N (%)		
Universal coverage	89 (91.8)	243 (80.7)
Civil Servant Medical Benefit and Social security scheme	5 (5.2)	44 (14.6)
Others	2 (2.1)	14 (4.7)
Being member of the PLHA self-help group: N (%)	56 (57.7)	182 (60.3)
History of previous treated with ART; N (%)	20 (20.6)	73 (24.3)
Mean time between HIV diagnosis and initiation of treatment: Years (SD)	10.7 (8.7)	5.2 (3.7)
Median duration of ART: Months (IQR)	7.4 (5.8-13.4)	7.7 (5.75-14.65)
Median baseline CD4 cell counts: cell/uL (IGR)	70 (22-153)	78.5 (26.5-171)

SD=standard deviation; IQR=inter-quartile range

Table 4-13: Changes of 97 participants' economic characteristics and other characteristics

Characteristics	Interview in 2004	Interview in 2007
Occupation; N (%)		
General labourer	60 (61.9)	55 (56.7)
Self employed	10 (10.3)	12 (12.4)
Farmer or gardener	9 (9.3)	8 (8.2)
Housewife	9 (9.3)	2 (2.1)
Others	9 (9.3)	17 (17.7)
Main wage earner; N (%)	59 (60.8)	53 (54.6)
Median monthly income: 1,000 THB (IQR)	3.0 (3.0-6.0)	3.0 (1.5-4.5)
Median monthly household income: 1,000 THB (IQR)	4.4 (2.5-6.9)	5.0 (3.5-8.0)
Median monthly household expenditure: 1,000 THB (IQR)	NA	4.5 (3.0-6.0)
Adherence more than 95%*		
In the past five days; N (%)	91 (93.8)	93 (95.9)
In the previous month; N (%)	95 (97.9)	96 (98.9)
ART regimen used: N (%)		
First line regimen ;GPO-Vir (d4T+3TC+NVP)	84 (86.6)	50 (51.5)
Alternate first line regimen; (d4T+3TC+EFV)	2 (2.1)	4 (4.1)
GPOz (AZT+3TC+NVP)	0	27 (27.8)
Others regimen	11 (11.3)	16 (16.6)

SD=standard deviation; IQR=inter-quartile range; NA=not applicable; GPO=Government Pharmaceutical Organisation; d4T=Stavudine; 3TC=Lamivudine; NVP=Nevirapine; EFV=Efavirenz;
* Accounted for missed dose only

In relation to socioeconomics, nearly all participants had remained in the same job between 2004 and 2007 and more than half of them were the main wage earner in the families. However, over the period of three years their monthly incomes are quite stable. In contrast, their average household income had risen (from 5,700 in 2004 to 6,500 in 2007). This appeared to indicate that other household members had become more economically active to compensate for their reduced earning capability. When asked about their expenditures, it appeared that their expenditures were in excess of their monthly income, leaving little money left each month.

Their adherence was also assessed in terms of self-reported adherence, with more than 90% of respondents reporting having taken more than 95% of doses of ART both in the past five days and in the previous month. This indicates that adherence in 2007 had increased compared to 2004 (see Table 4-13). The regimens of prescribed ART had also been adjusted; in 2004, GPO-Vir was the dominant treatment, however, in 2007, only half of them were still on this regimen. Another half the participants were prescribed with alternative regimens to GPO-Vir as they either experienced side effects or had required

transfer to second line therapy (see Table 4-13). For further details of changes in prescribed regimens, please refer to section 4.1.5

4.1.2.3 Modified McGill Questionnaire

Two questionnaires were used to determine patient's health-related quality of life; modified McGill's questionnaire and EQ-5D (Thai version) in order to measure the impact of the government ART programme on the patient's emotional, social and physical wellbeing. For the modified McGill's questionnaire, participants answered each question with the range of Level I to Level V with Level I (floor score) indicating extremely bad, and Level V (ceiling score) indicating extremely good. The questions consisted of two single-item scale (SIS) questions and 16 sub-measure questions. The two summary SIS questions were used to ask the participant to assess their overall quality of life in the past two days and their comparative quality of life in the past two days compared to just before starting ART. The other 16 questions were used to address individual aspects of HR-QOL in sub-dimensions.

Table 4-14: HR-QOL using Modified McGill questionnaire-single question

Modified McGill Questionnaire, Single question	Interview in 2004: N (%)	Interview in 2007: N (%)	P value
Overall quality of life in the past two days			0.24
Level I (Very bad)	3 (3.1)	4 (4.1)	
Level II	13 (13.4)	8 (9.3)	
Level III	51 (52.6)	50 (51.5)	
Level IV	22 (22.7)	32 (33.0)	
Level V (Excellent)	8 (8.2)	3 (3.1)	
Overall quality of life in the past two days comparing to before entering the governmental antiretroviral treatment programme			0.76
Level I (Extremely worse)	0	0	
Level II	2 (2.1)	2 (2.1)	
Level III	17 (17.5)	12 (12.4)	
Level IV	59 (60.8)	62 (63.9)	
Level V (Extremely better)	19 (19.6)	20 (20.6)	

Approximately 80% of the respondents, when asked to rate their HR-QOL over the period of 3 years on ART, stated that their health status was Level III, IV or V (Level V =excellent). When they were asked to compare their current health status with that experienced before initiation of ART, more than 80% reported feeling Level IV or V (Level

V=extremely better). This pattern was observed in both surveys (see Table 4-14) with no statistical differences between the two interviews.

Table 4-15: Physical well being using modified McGill questionnaire

Physical well being in the past 2 days…	Interview in 2004: N (%)	Interview in 2007: N (%)	P value
Level of trouble some physical symptom 1(if any)			0.26
Level I (No problem)	65 (67.0)	61 (62.9)	
Level II	18 (18.6)	21 (21.6)	
Level III	11 (11.3)	15 (15.5)	
Level IV	3 (3.1)	0	
Level V (Tremendous)	0	0	
Level of trouble some physical symptom 2 (if any)			0.18
Level I (No problem)	87 (89.7)	78 (80.4)	
Level II	3 (3.1)	10 (10.3)	
Level III	5 (5.2)	5 (5.2)	
Level IV	2 (2.1)	4 (4.1)	
Level V (Tremendous)	0	0	
Level of trouble some physical symptom 3 (if any)			0.95
Level I (No problem)	93 (95.9)	92 (94.8)	
Level II	2 (2.1)	2 (2.1)	
Level III	1 (1.0)	2 (2.1)	
Level IV	1 (1.0)	1 (1.0)	
Level V (Tremendous)	0	0	
I have felt that my physical is			0.39
Level I (extremely weak)	0	2 (2.1)	
Level II	4 (4.1)	8 (8.2)	
Level III	33 (34.0)	34 (35.1)	
Level IV	55 (56.7)	50 (51.5)	
Level V (very well)	5 (5.2)	3 (3.1)	

Table 4-16: Psychological status using modified McGill questionnaire

Psychological status in the past 2 days…	Interview in 2004: N (%)	Interview in 2007: N (%)	P value
I have been depressed			0.17
Level I (not at all)	74 (76.3)	65 (67.0)	
Level II	17 (17.5)	28 (28.9)	
Level III	4 (4.1)	3 (3.1)	
Level IV	2 (2.1)	0	
Level V (extremely)	0	1 (1.0)	
I have been nervous or worried			0.14
Level I (not at all)	61 (62.9)	45 (46.4)	
Level II	21 (21.6)	27 (27.8)	
Level III	7 (7.2)	15 (15.5)	
Level IV	5 (5.2)	8 (8.2)	
Level V (extremely)	3 (3.1)	2 (2.1)	
How much of the time did you feel sad			0.22
Level I (never)	56 (57.7)	64 (66.0)	
Level II	35 (36.1)	26 (26.8)	
Level III	1 (1.0)	4 (4.1)	
Level IV	4 (4.1	1 (1.0)	
Level V (always)	1 (1.0)	2 (2.1)	
When I thought of the future, I was			0.90
Level I (not afraid)	44 (45.4)	44 (45.4)	
Level II	29 (29.9)	29 (29.9)	
Level III	14 (14.4)	12 (12.4)	
Level IV	4 (4.1)	7 (7.2)	
Level V (terrified)	6 (6.2)	5 (5.2)	

Tables 4-15 to Table 4-18 provide details of the sub-measures of the Modified McGill Questionnaire used to evaluate the physical well being, psychological status, existential feeling and support received by participants respectively. All of these were unchanged between the two interviews, except certain questions related to emotional well being which showed that fewer participants reported negative feeling in 2007 (see Table 4-17). In both interviews, more than 80% of respondents reported their physical well being as level III, IV or V (Table 4-15). The questionnaire requested the patients to provide three physical symptoms they had experienced during the past two days. The frequently noted symptoms were feeling weary, numbness, hearing difficulty, rash, tremor and body pain, however, these caused only limited problems for them. Regarding their psychological status (Table 4-15), there were also no significant differences between the two interviews in relation to level of depression, nervousness or worry, time of feeling sad and their fear with regard to the future.

Table 4-17: Existential feeling using modified McGill questionnaire

Existential feeling in the past 2 days	Interview in 2004: N (%)	Interview in 2007: N (%)	P value
My life has been			0.006
Level I (utterly meaningless and without purpose)	2 (2.1)	0	
Level II	19 (19.6)	8 (8.2)	
Level III	38 (39.2)	28 (28.9)	
Level IV	30 (30.9)	42 (43.3)	
Level V (purposeful and meaningful)	8 (8.2)	19 (19.6)	
When I thought about my whole life, I felt that in achieving life goals I have			0.001
Level I (made no progress whatsoever)	12 (12.4)	7 (7.2)	
Level II	37 (38.1)	9 (9.3)	
Level III	38 (39.2)	53 (54.6)	
Level IV	7 (7.2)	26 (26.8)	
Level V (progressed to complete fulfilment)	3 (3.1)	2 (2.1)	
When I thought about my life, I felt that my life to this point has been			0.51
Level I (completely worthless)	5 (5.2)	4 (4.1)	
Level II	8 (8.2)	10 (10.3)	
Level III	62 (63.9)	51 (52.6)	
Level IV	17 (17.5)	24 (24.7)	
Level V (very worthwhile)	5 (5.2)	8 (8.2)	
I have felt that I have			0.50
Level I (no control over my life)	0	1 (1.0)	
Level II	12 (12.4)	6 (6.2)	
Level III	48 (49.5)	53 (54.6)	
Level IV	33 (34.0)	32 (33.0)	
Level V (completely control over my life)	4 (4.1)	5 (5.2)	
I felt good about myself as a person			0.49
Level I (completely disagree)	4 (4.1)	1 (1.0)	
Level II	65 (67.0)	1 (1.0)	
Level III	21 (21.6)	65 (67.0)	
Level IV	7 (7.2)	19 (19.6)	
Level V (complete agree)	0	10 (10.3)	
The past 2 days were			0.08
Level I (burden)	2 (2.1)	1 (1.0)	
Level II	12 (12.4)	3 (3.1)	
Level III	69 (71.1)	70 (72.2)	
Level IV	13 (13.4)	20 (20.6)	
Level V (a gift)	1 (1.0)	3 (3.1)	

Six questions addressed their existential feeling (see Table 4-17). The responses identified that patients tended to have improved relation to their feelings about their life and the achieving of goals in their lives (statistical significant; p=0.006 and 0.001 respectively)

between 2004 and 2007. However, their answers were similar between the two interviews regarding other questions in this sub-measure. In terms of their perceived support structures, they felt less supported in 2007 however; this did not achieve statistical significance (see Table 4-18)

Table 4-18: Evaluation of support using modified McGill questionnaire

Support in the past 2 days	Interview in 2004: N (%)	Interview in 2007: N (%)	P value
The world has been			0.09
Level I (an impersonal unfeeling place)	1 (1.0)	1 (1.0)	
Level II	79 (81.4)	6 (6.2)	
Level III	12 (12.4)	64 (66.0)	
Level IV	5 (5.2)	19 (19.6)	
Level V (caring and responsive to my needs)	0	7 (7.2)	
I have felt supported			0.09
Level I (not at all)	0	29 (29.9)	
Level II	27 (27.8)	19 (19.6)	
Level III	19 (19.6)	27 (27.8)	
Level IV	39 (40.2)	17 (17.5)	
Level V (completely)	12 (12.4)	5 (5.2)	

4.1.2.4 EQ-5D

Table 4-19: HR-QOL using EQ-5D

EQ-5D	Interview in 2004: N (%)	Interview in 2007: N (%)	P value
Mobility			0.09
I have no problems in walking about	82 (84.5)	89 (91.8)	
I have some problems in walking about	15 (15.5)	8 (8.2)	
I am confined to bed	0	0	
Self-Care			0.00
I have no problems with self-care	95 (97.9)	66 (68.0)	
I have some problems washing or dressing myself	2 (2.1)	31 (32.0)	
I am unable to wash or dress myself	0	0	
Usual activities (e.g. Work, study, housework family or leisure activities)			0.11
I have no problems with performing my usual activities	90 (92.8)	83 (85.6)	
I have some problems with performing my usual activities	6 (6.2)	14 (14.4)	
I am unable to perform my usual activities	1 (1.0)	0	
Pain/Discomfort			0.07
I have no pain or discomfort	65 (67.0)	51 (52.6)	
I have moderate pain or discomfort	31 (32.0)	45 (46.4)	
I have extreme pain or discomfort	1 (1.0)	1 (1.0)	
Anxiety/Depression			0.80
I am not anxious or depressed	65 (67.0)	79 (81.4)	
I am moderately anxious or depressed	31 (32.0)	18 (18.6)	
I am extremely anxious or depressed	1 (1.0)	0	
Median of visual analogue scale: IQR	80 (70-90)	80 (70-90)	0.74

IQR=Inter-quartile range

In relation to EQ-5D, the five dimensions were found to be unchanged between the two interviews in term of mobility, usual activities, pain/discomfort and anxiety/depression. However, in the area of self care, more participants reported having experienced additional problems washing or dressing themselves in 2007 (see Table 4-19). The overall evaluation of HR-QOL assessed in the visual analogue scale did not experience any significant change (see Table 4-20). However, using the index score, it was found that the median of the score

in 2007 was like to be lower than that identified in 2004 (statistically significant, Wilcoxon Signed Ranks test, p=0.001).

Table 4-20: Descriptive statistics of EQ-5D index scores using Japan* preference weights

EQ-5D	Mean	SD	Median	Q25	Q75
EQ-5D index score					
In 2004	0.90	0.12	0.85	0.81	1.00
In 2007	0.85	0.12	0.83	0.78	0.83
VAS					
In 2004	78.64	16.07	80.00	70.00	90.00
In 2007	77.99	17.79	80.00	70.00	90.00

*Japanese weight was used as (i) Thai weight was not available and (ii) it has been shown by one study that the Japanese weight is more preferable psychometric property than that of the US, and the UK model (Sakthong 2008)

When we compared the HR-QOL reported by each individual to identify who were better off or worse off from the ART programme, it has found that majority of the people reported an unchanged quality of life in nearly all dimensions of HR-QOL (see Table 4-21). However, the number of people who reported improvements as a consequence of ART was fewer than respondents who reported feeling worse off in nearly all dimensions of the questionnaires except for the VAS and index score of the EQ-5D where more than 40% of the participants reported of better off as time elapsed

Table 4-21: Intra-person comparison of HR-QOL from two interviews (2004 and 2007) using the Modified McGill Questionnaire

Health-related quality of life questionnaire	Number of people reported as*: N (%)		
	Worse off	No changes	Better off
Single question			
▪ Overall quality of life in the past two days	26 (26.8)	44 (44.4)	27 (27.8)
▪ Overall quality of life in the past two days comparing to before entering the programme	28 (28.7)	47 (48.5)	22 (22.8)
Sub dimension			
Physical well being			
▪ Level of physical symptom 1 (if any)	24 (24.7)	52 (53.6)	21 (21.7)
▪ Level of physical symptom 2 (if any)	15 (15.4)	73 (75.3)	9 (9.3)
▪ Level of physical symptom 3 (if any)	4 (4.1)	90 (92.8)	3 (3.1)
▪ I have felt that my physical is	16 (16.5)	54 (55.7)	27 (28.7)
Psychological status			
▪ I have been depressed	21 (21.6)	62 (63.9)	14 (14.5)
▪ I have been nervous or worried	34 (35.0)	51 (52.6)	12 (12.4)
▪ How much of the time did you feel sad	15 (15.4)	62 (63.9)	20 (20.6)
▪ When I thought of the future, I was	28 (28.9)	41 (42.2)	28 (28.9)
Existential feeling			
▪ My life has been	48 (29.5)	26 (26.8)	23 (23.7)
▪ When I thought about my whole life, I felt that in achieving life goals I have	53 (54.6)	26 (26.8)	18 (18.6)
▪ When I thought about my life, I felt that my life to this point has been	31 (31.8)	45 (46.4)	21 (21.7)
▪ I have felt that I have	30 (30.9)	42 (43.3)	25 (25.8)
▪ I felt good about myself as a person	21 (21.6)	60 (61.9)	16 (16.5)
▪ The past 2 days were	24 (24.8)	65 (67.0)	8 (8.2)
Support			
▪ The world has been	20 (20.6)	59 (60.8)	18 (18.6)
▪ I have felt supported	38 (39.1)	27 (27.8)	32 (33.0)

* Compared with the participants reported in the interview in 2004;

Table 4-22: Intra-person comparison of HR-QOL from two interviews (2004 and 2007) using EQ-5D

Health-related quality of life questionnaire	Number of people reported as*: N (%)		
	Worse off	No changes	Better off
EQ-5D			
▪ Mobility	5 (5.1)	80 (82.5)	12 (12.4)
▪ Self-Care	36 (37.1)	60 (61.9)	1 (1.0)
▪ Usual activities	12 (12.4)	80 (82.5)	5 (5.1)
▪ Pain/Discomfort	27 (27.8)	59 (60.8)	11 (11.3)
▪ Anxiety/Depression	12 (12.4)	59 (60.8)	26 (26.8)
▪ VAS	35 (36.1)	2 (21.6)	41 (42.3)
▪ Index score	25 (25.8)	22 (22.7)	40 (51.5)

4.1.3 Improvement of the CD4 cell count

As many as 271 participants with a baseline CD4 cell count of less than 200 cell/uL were found to also have CD4 cell counts above 200 cell/uL during the follow up period. Of these 271, their mean age was 36.2 years old (SD=7.0), and about 42% of them were male. For their health insurance status, roughly 90% were in the universal health scheme and about 63% of them were the members of PLHA self-help groups. In relation to their clinical information, 30% of them were in WHO stage I, II or III. Their median baseline CD4 cell count was 92 cell/uL and nearly all were prescribed initially with NNRTI-based regimen. Moreover, only 70% of patients were naïve to treatment. Time to event analysis revealed that their median time from the initiation of ART to exhibiting a CD4 cell count of below 200 cell/uL was 33.6 months (SD=3.6) while the mean time was 44.4 months (SD=1.7). The hazard function in Table 4-4 suggests a constancy of risk during the follow up period.

4.1.4 CD4 approached the level of 500 cell/ μL

Achieving a CD4 cell count of 500 cell/uL was used to assess the effect of ART on immune recovery as this level of CD4 cell count can effectively protect the patients from possible opportunistic infections. During this follow up period, 121 participants with baseline CD4 cell counts below 500 cell/uL developed CD4 cell counts above 500 cell/uL. Their characteristics were similar to those identified in the patients who developed CD4 counts of 200 cell/uL or more. Their mean age was 36 years (SD=7.0) and most were female (69%).

About 63% were members of PLHA self-help groups, and most of them were in UCS. In relation to clinical information, nearly 60% were naïve to treatment, and half were in Stage IV at baseline. The median of their baseline CD4 cell counts were 154 cell/uL (IQR=47-335) which was relatively high compared to the rest of the participants, and most of them (85%) were prescribed initially with NNRTI-based regimen. From the time to event analysis, the mean time of CD4 cell counts from the initiation of ART to reach the level of 500 cell/uL was 75.7 months (SE=1.9) with a constant risk of the increase of CD4 cell counts over the follow up period (see Table 4-4).

4.1.5 Duration on the first-line regimen

During this three year period of analysis, prescribed regimens were changed in 157 participants. The two main reasons for changing treatment regimen were that the patients either developed drug resistance or experienced adverse events. Of these 157, their average age was 36 years old (SD=7.1) and most were female (62.4%). More than 80% of them were in the universal health scheme and only half of them were members of PLHA self-help groups. In relation to clinical information, nearly 60% of them were naïve to ART and about 55% of them were in stage IV of WHO classification. Their baseline CD4 cell counts were 116 cell/uL and 90% were initially prescribed with NNRTI-based regimen. About half of them were from the large nurse-led clinic, 30% from doctor-led clinic and 20% were from the small nurse-led clinic. In relation to time since initiation of treatment to alteration of regimen (time to event analysis), the median time on the first regimen was 73.9 months (SD=8.3) while the mean time was 64.3 months (SD=1.9) (see Table 4-4).

4.1.5.1 Development of adverse reaction

The two main reasons for changing the prescribed regimen were (i) occurrence of an adverse reaction from ART and (ii) development of drug resistance. For the former category, it was found that 93 cases experienced adverse reaction. Nearly 50% were lipodystrophy which usually caused by the stavudine in the GPO-Vir (3TC+d4T+NVP) and had to substitute with zidovudine (see Table 4-23). Another common side effect was severe

rash which is common caused by nevirapine and had to change to the alternative first-line regimens including AZT+d4T+NVP, AZT+3TC+EFV, EFV+IDV+RTV or AZT+3TC +SQV+RTV. When we analyzed the quality of life comparing those who reported experiencing side effects and those who did not, it was found that the quality of life measured by Modified McGill and EQ-5D questionnaire were similar between the groups (Chi square test > 0.05). But, again this was based solely on the 97 participants who were interviewed for their HR-QOL.

Table 4-23: Adverse reactions

Adverse reaction	N (%)
Lipodystrophy	44 (8.8)
Severe rash	26 (5.2)
Hepatitis	10 (2.0)
Others	13 (2.6)
Total	93 (18.6)

4.1.5.2 Drug resistance

In the national ART programme, those who have been treated with ART for over a year and (i) develop new opportunistic infections, (ii) no rise or falling of CD4 cell counts and (iii) viral load more than 1,000 copy/ml are suspected of developing drug resistance and will be sent for a test of HIV drug resistance. Two types of test are used: Ultrasense Cobas Amplicor HIV-1 and TRUEGENE HIV-1 Genotyping in case of viral load higher than 2,000 copy/ml (Srasuebkul, Ungsedhapand et al. 2007).

Twenty-four participants developed drug resistance which was initially indicated by a worsened clinical presentation (e.g. high viral load despite treatment, advance staging, developing new opportunistic infection) and ultimately confirmed by the test for drug resistance during the period of the study. Their average age 33 years (SD=8.0) and fourteen of them were male. For their clinical information, seven cases were naïve to treatment and their baseline CD4 cell counts were 180 cell/uL. Almost all (21 cases) were in stage IV and the majority were prescribed NNRTI-based regimen.

4.1.5.3 Other causes of changing drug regimen

A range of other reasons were identified for altering drug regimen. These included; (i) patients with allergies to some drugs such as nevirapine, (ii) patients developed tuberculosis during treatment, the regimens then were adjusted to avoid toxicity, (iii) after finishing treating tuberculosis, the patients were switched back to their previous regimens and (iv) the first phase of ART programme (2001-2002) was ended, during the phrase, the patients were prescribed with one of eight regimens which was reduced to 3 recommended regimens as the programme expanded.

4.1.6 Other treatment outcomes

Changing of WHO staging; for this treatment outcome, only 13 cases were found to have disease progression defined by an advance in WHO staging (see Table 4-24). This low event rate is largely due to the fact that more than 90% of the participants were already in stage IV and therefore the survival analysis was not appropriate to apply for this outcome. Of these 13, their average age was 35 years (SD=6.7) and nine of them were male. In relation to clinical information, eight of them had previous experience of ART. Their mean baseline CD4 cell counts were relatively high (259 cell/uL) as they were in either Stage II or III before the disease progressed. Twelve of them were initially prescribed with NNRTI-base regimen. Ten patients whose disease progressed were treated in the doctor-led clinical. No patients treated in the small nurse-led clinics were identified as suffering deterioration in terms of WHO staging.

Table 4-24: Disease progression determined by changing of WHO classification

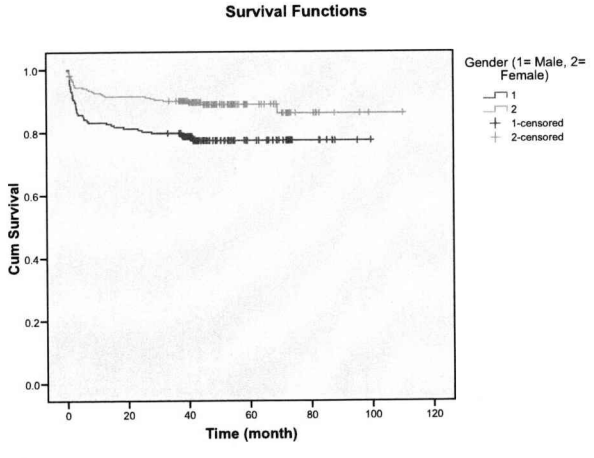
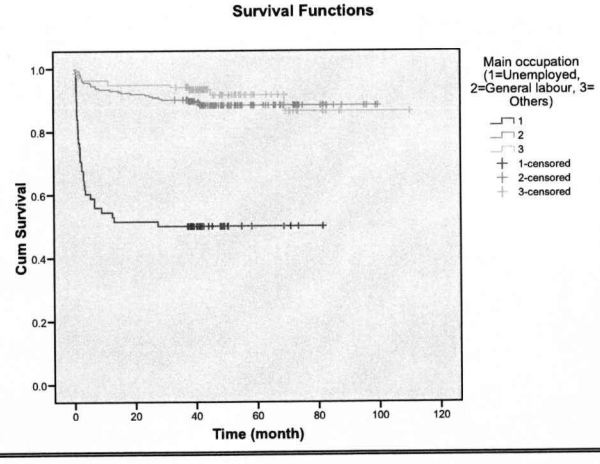
WHO staging	N
From stage II to stage III	3
From stage II to stage IV	2
From stage III to stage IV	8

4.2 Factors affecting the treatment outcomes

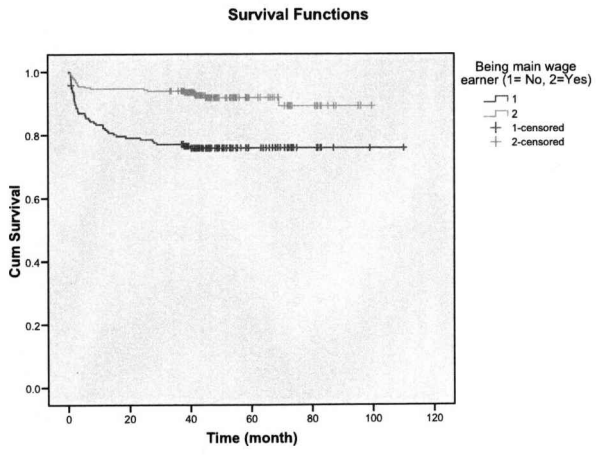
4.2.1 Factors affecting mortality (survival)

Out of 15 potential variables that would affect the patients' survival, using the log rank test which is a nonparametric test to compare the survival distributions of groups; it was found that participants tended to die faster if they were male, unemployed, not a main wage earner, no income, treated under universal health scheme (USC), naive to ART, having a baseline CD4 cell count less than 50 cell/uL, in Stage IV at baseline, and initially treated with PI-based regimen and being treated in nurse-led clinics.

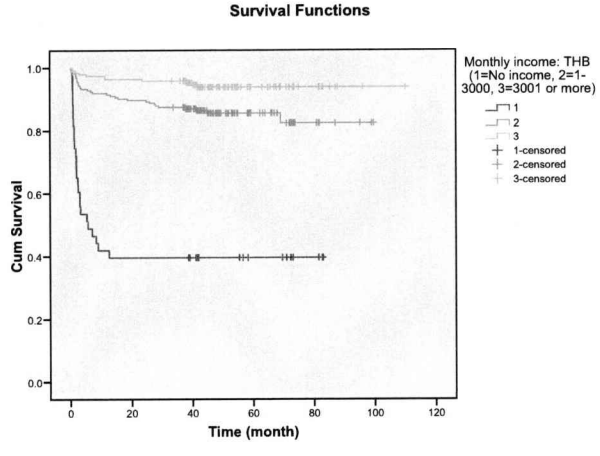
Table 4-25: Log rank test for factors affecting mortality

Predictor	Survival function	P-value
Gender		0.001*
Main occupation		0.000*

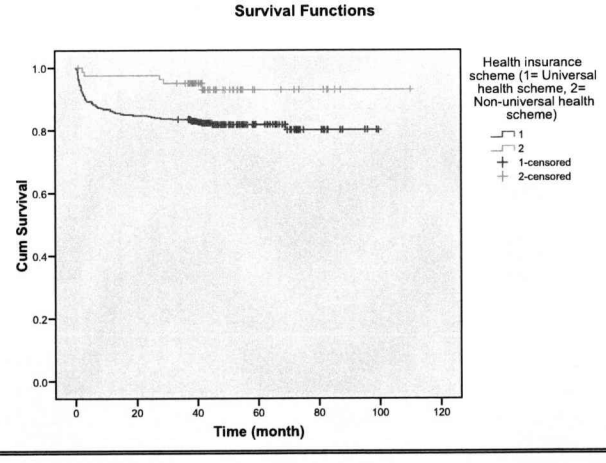
Being Main wage earner 0.000*



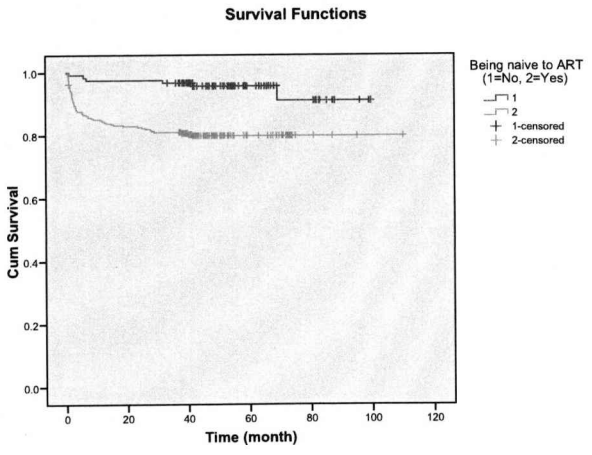
Monthly income: THB 0.000*



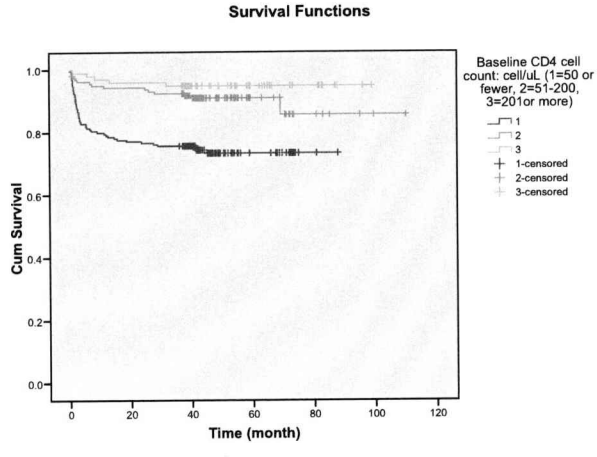
Health insurance scheme 0.01*



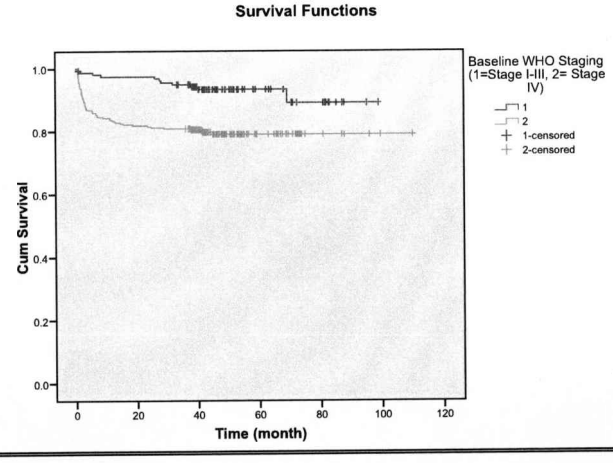
Being naïve to ART 0.000*



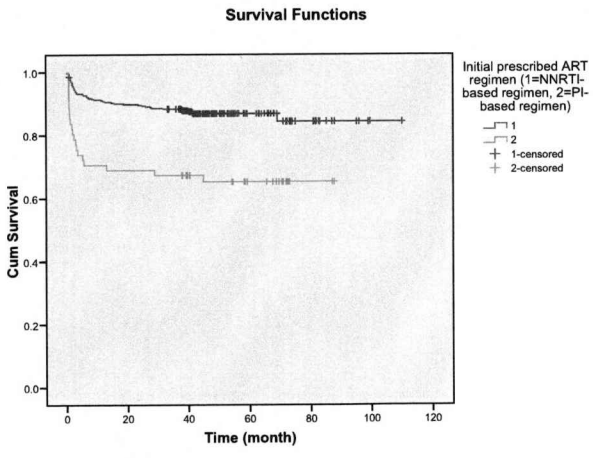
Baseline CD4: cell/μL 0.000*



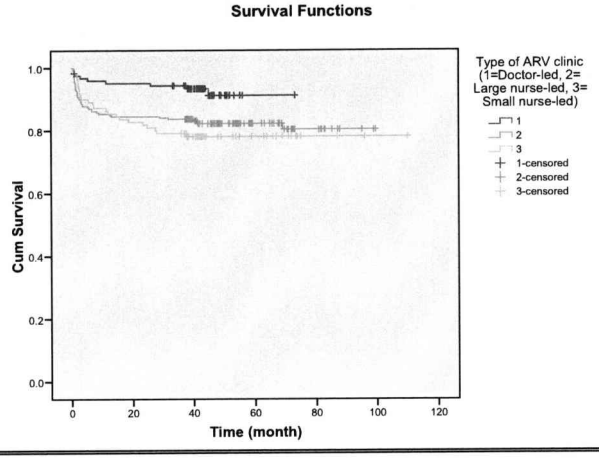
Baseline WHO staging 0.000*



Initial prescribed regimen 0.000*



Type of ARV clinic 0.009*



*=Significant at p value<0.05
** Full details of Log Rank test for this outcome are provided in Annex 2

The Cox proportional hazard regression is based on a modelling approach to the analysis of survival data. The purpose of the model is to simultaneously explore the effects of several variables on survival. It allows us to isolate the effects of interesting factors from the effects of other variables. From the Cox model of survival of 501 participants, it identified being male, unemployed, being a general labourer and low household income as leading to lower survival and with being a member of PLHA self-help group were associated with higher mortality while being treated in a doctor-led or large nurse-led clinic leading to greater survival. Full details of the Log Rank test and Cox proportional hazard regression for CD4 cell counts are provided in Annex 2

Table 4-26: Cox proportional hazard regression for mortality*

Variable	Regression coefficient	Hazard ratio	P value
Male	0.64	1.90	0.04*
Main occupation			
Unemployed	2.61	13.65	0.000*
General labourer	1.52	4.56	0.015*
Monthly income	0.001	0.99	0.000*
Being member of PLHA self-help group	0.84	2.31	0.005*
Type of ARV clinic			
Doctor-led	-2.35	0.10	0.002*
Large nurse-led	-1.28	0.27	0.002*

*=Significant at p value<0.05
**Full details of Cox model for this outcome are provided in Annex 2

4.2.2 Factors determining changes in quality of life

A bi-variate analysis was undertaken to identify factors that might influence changes in HR-QOL (worse off, no changes, better off). No variable appeared to be associated with the change in quality of life using the first question of Modified McGill questionnaire which asked the participants to rate the overall quality of life in the past two days at the time of interview. However, when using EQ-5D visual analogue scale, it was found that being a member of PLHA self help group was strongly associated with improvements in self-reported quality of life (Chi square test, p=0.027) (see Table 4-27).

Table 4-27: P-values of factors determining changes HR-QOL from bi-variate analysis

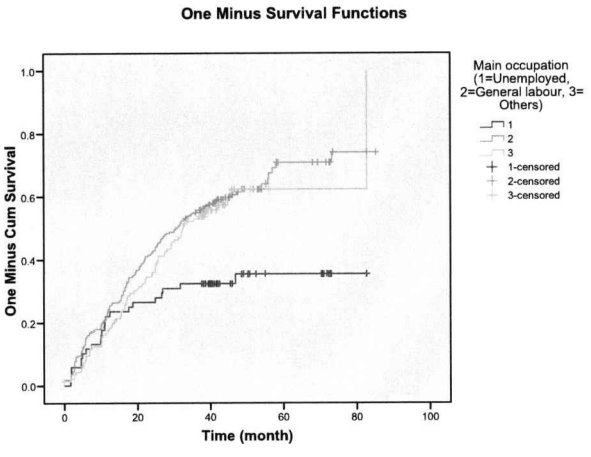
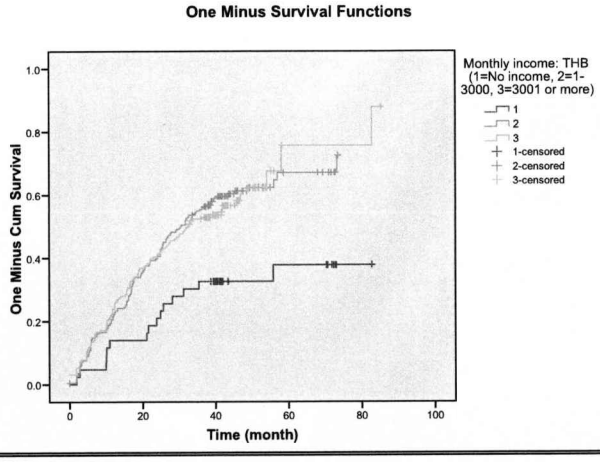
Variable	Overall health in the past 2 day (Modified McGill Questionnaire); P-value	EQ-5D visual analogue scale (VAS); P-value
Gender	0.71	0.76
Age	0.86	0.93
Main occupation	0.47	0.82
Being main wage earner	0.41	0.45
Monthly income	0.49	0.20
Monthly household income	0.15	0.27
Education	0.32	0.51
Health insurance scheme	0.77	0.79
Distance from the hospitals to their houses	0.16	0.97
Being PLHA self-help group member	0.78	0.027*
Being naïve to the ART	0.12	0.57
Baseline CD4 cell counts	0.15	0.96
Baseline WHO staging	0.14	0.23
Initial prescribed ART	0.29	0.73
Type of ARV clinic	0.11	0.26

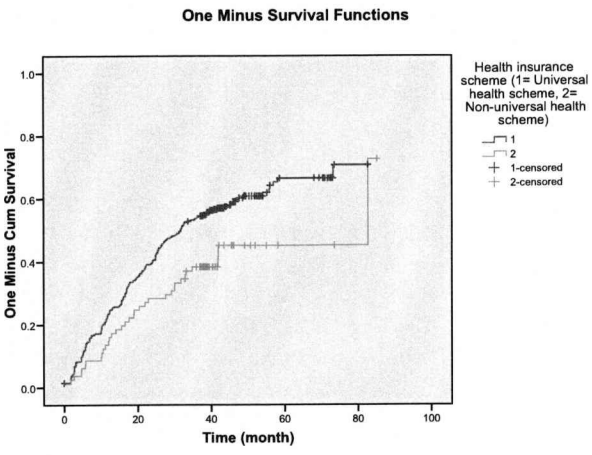
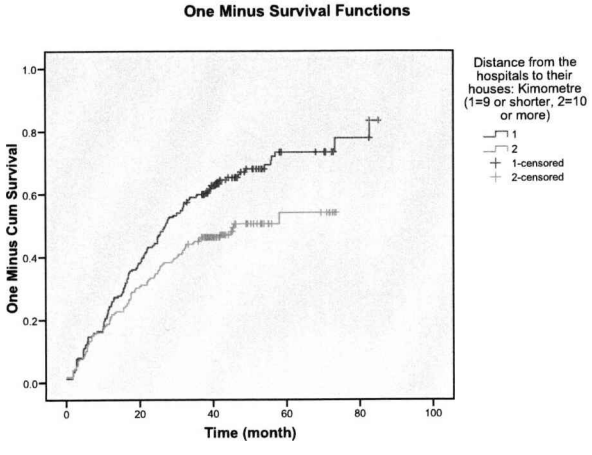
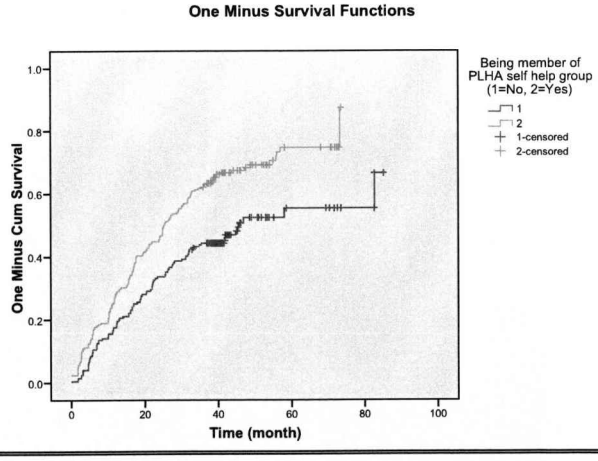
4.2.3 Factors affecting improvement of the CD4 cell count

4.2.3.1 CD4 cell count approached the level of 200 cell/uL

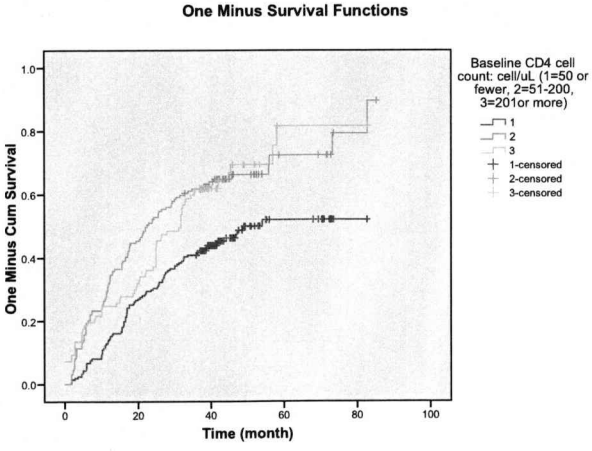
To identify the effect of the interesting variables on this outcome using the log rank test, it was found that participants who were employed, with high income, being under the USC, lived near the hospitals, being member of PLHA, with high baseline CD4 cell count and being treated in the nurse-led clinics would develop CD4 cell counts of 200 cell/uL faster significantly.

Table 4-28: Log rank test for factors affecting improvement of the CD4 count approached the level of 200 cell/uL

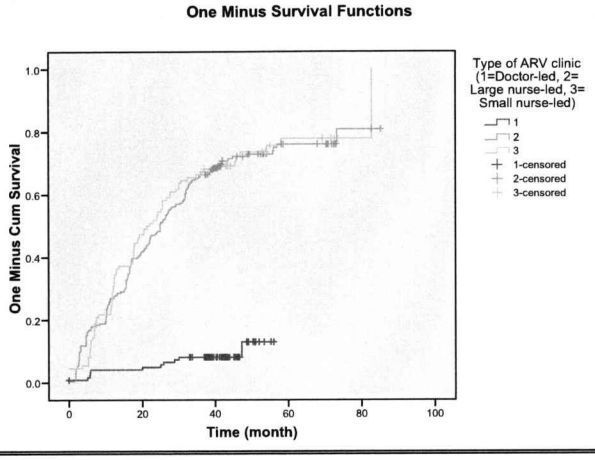
Predictor	Time to event (1-survival)function	P-value
Main occupation		0.001*
Monthly income: THB		0.005*

Health insurance scheme		0.009*
Distance between hospitals and their houses: Kilometre		0.001*
Being member of people who living with HIV/AIDS (PLHA) self-help group		0.000*

Baseline CD4: cell/μL	0.000*



Type of ARV clinic	0.000*



*=Significant at p value<0.05

** Full details of Log Rank test for this outcome are provided in Annex 2

To eliminate the confounding influence from the other factors using the Cox proportional hazard regression, being employed, being a general labourer, being a member of PLHA self help group, having higher monthly income or household income, being naïve to treatment and being treated in nurse-led clinic were found to be associated with better response of CD4 cell count (faster to reach the level of 200 cell/uL). Full details of the Log Rank test and Cox proportional hazard regression for CD4 cell counts are provided in Annex 2.

Table 4-29: Cox proportional hazard regression for having CD4 approached the level of 200cell/uL

Variable	Regression coefficient	Hazard ratio	P value
Main occupation			
Unemployed	-0.71	0.49	0.011*
General labourer	-0.38	0.68	0.018*
Monthly income	0.001	0.99	0.008*
Monthly household income	0.001	0.99	0.033*
Being member of PLHA self-help group	0.35	1.42	0.018*
Being naïve to the ART	0.37	1.45	0.034*
Baseline CD4 cell counts	0.44	1.56	0.000*
Type of ARV clinic			
Doctor-led	-2.68	0.07	0.000*
Large nurse-led	-0.10	0.90	0.57

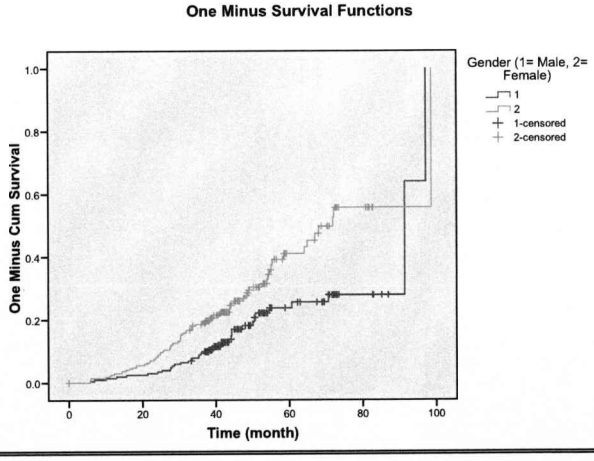
*=Significant at p value<0.05

** Full details of Cox model for this outcome are provided in Annex 2

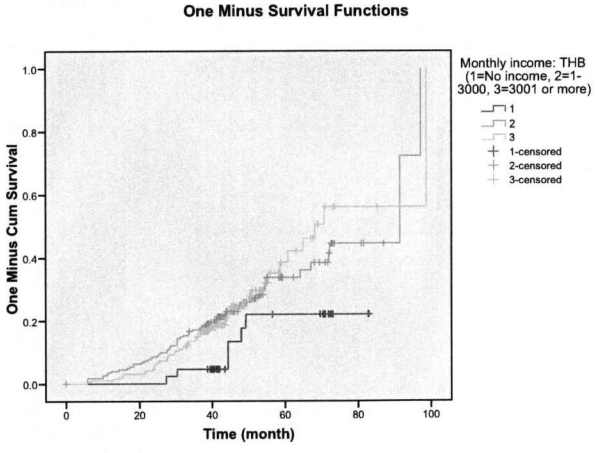
4.2.3.2 CD4 cell count approached the level of 500 cell/uL

From the log rank test, it was found that being women, high income, previous treatment with ART, high CD4 cell counts at baseline, being in the WHO stage I, II or III at baseline and being treated by the nurse-led clinics tended to approach the level of 500 cell/uL faster.

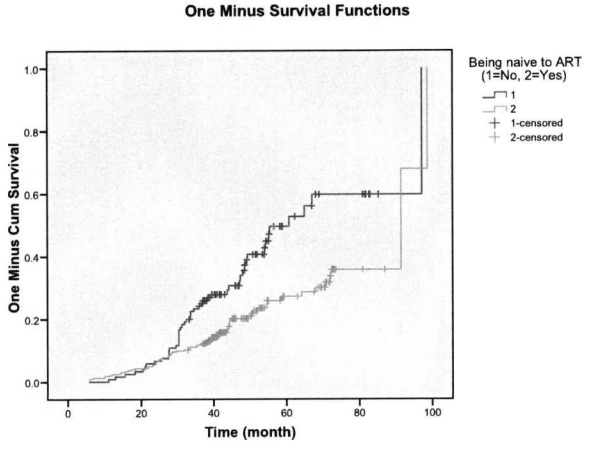
Table 4-30: Log rank test for factors affecting improvement of the CD4 count approached the level of 500 cell/uL

Predictor	Time to event (1-survival)function	P-value
Gender		0.001*

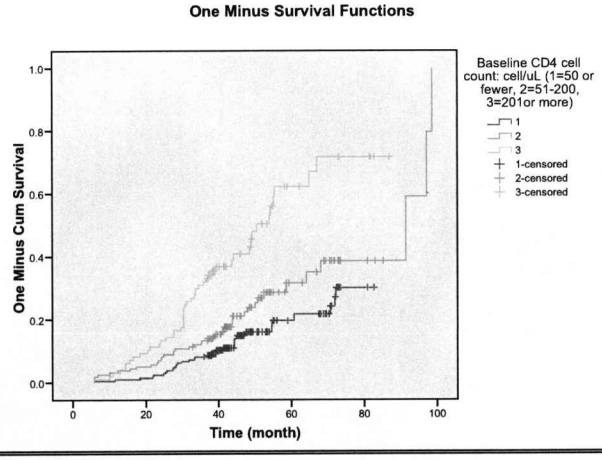
Monthly income: THB 0.048*



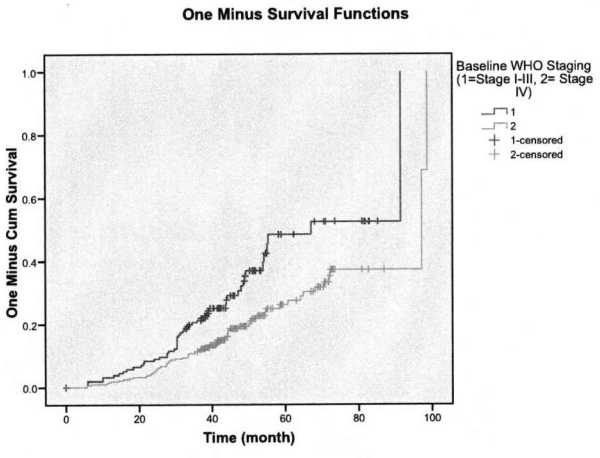
Being naïve to ART 0.000*



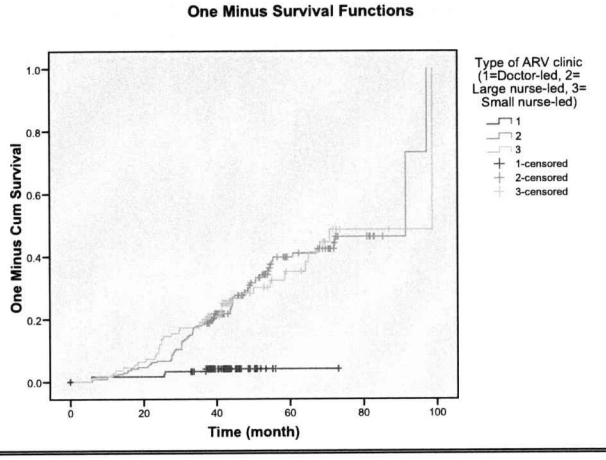
Baseline CD4: cell/μL 0.000*



Baseline WHO staging	0.001*



Type of ARV clinic	0.000*



*=Significant at p value<0.05

** Full details of Log Rank test for this outcome are provided in Annex 2

To eliminate the confounding influence from the other factors using the Cox proportional hazard regression, being female, with high baseline CD4 cell count and being treated in small nurse-led clinic were associated with faster response of CD4 cell counts to achieve the level of 500 cell/uL. Full details of the Log Rank test and Cox proportional hazard regression for CD4 cell counts approaching the level of 500 cell/uL are provided in Annex 2.

Table 4-31: Cox proportional hazard regression for having CD 4 count approached the level of 500 cell/uL

Variable	Regression coefficient	Hazard ratio	P value
Male	-0.63	0.53	0.004*
Baseline CD4 cell counts	0.60	1.82	0.000*
Type of ARV clinic			
Doctor-led	-2.66	0.07	0.000*
Large nurse-led	-0.29	0.75	0.33

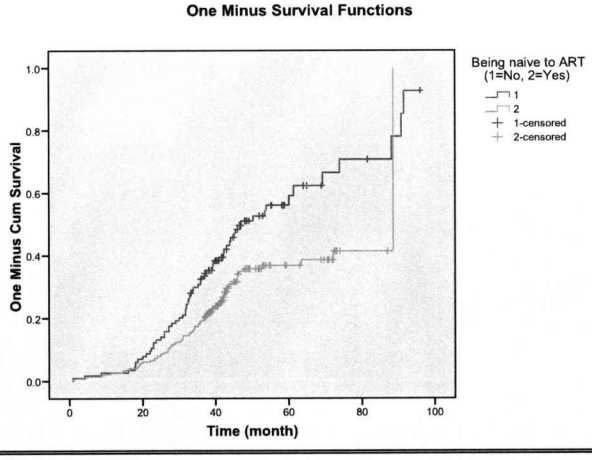
*=Significant at p value<0.05

** Full details of Cox model for this outcome are provided in Annex 2

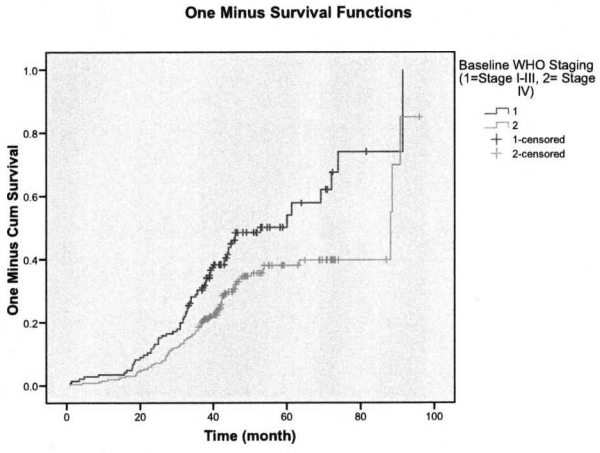
4.2.4 Factors affecting duration on the first-line regimen

From the Log rank test, it was found that participants who used to be treated with other ARV drugs, Stage IV WHO classification at baseline, being prescribed with NNRTI-based regimen and being treated in the doctor-led clinic made it more probable that their regimen would be changed

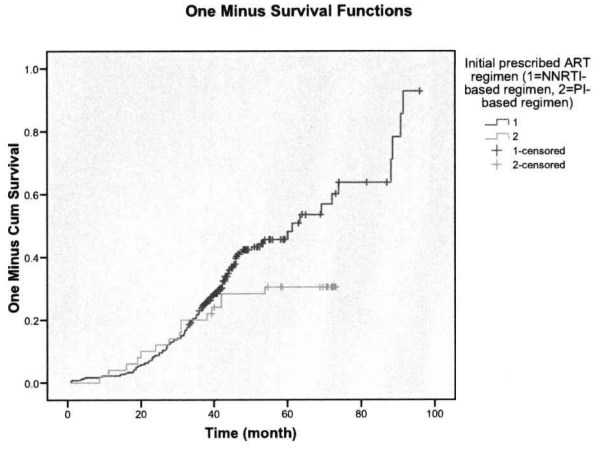
Table 4-32: Log rank test for factors affecting duration on the first-line regimen

Predictor	Time to event (1-survival)function	P-value
Being naïve to ART		0.001*

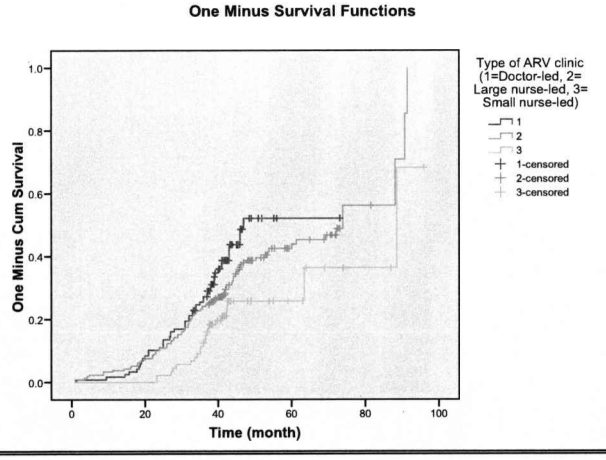
Baseline WHO staging 0.001*



Initial prescribed regimen 0.028*



Type of ARV clinic 0.014*



*=Significant at p value<0.05

** Full details of Log Rank test for this outcome are provided in Annex 2

To eliminate the confounding influence from the other factors using the Cox proportional hazard regression, it was found that only being treated in a doctor-led clinic was associated with an increased probability of changing of treatment regimen (see Table 4-33).

Table 4-33: Cox proportional hazard regression for factor affecting duration on the first-line regimen*

Variable	Regression coefficient	Hazard ratio	P value
Type of ARV clinic			
Doctor-led	0.82	2.28	0.006*
Large nurse-led	0.46	1.58	0.11

*=Significant at p value<0.05

** Full details of Cox model test for this outcome are provided in Annex 2

4.3 Summary of the main factor affecting the outcomes

Table 4-34 gives the summarisation of the *p-values* from the analysis of the 15 potential baseline characteristic that might associate with the four treatment outcomes using Cox proportional hazard regression.

Table 4-34: P-values from Cox proportional hazard regression of patients' baseline characteristics predicting four outcomes

Variable	Mortality	CD4 approached 200 cell/uL	CD4 approached 500 cell/uL	ART regimen changed**
Male	0.04*	0.26	0.004*	0.97
Age	0.52	0.58	0.90	0.05
Main occupation				
Unemployed	0.000*	0.011*	0.58	0.26
General labourer	0.015*	0.018*	0.04	0.23
Being main wage earner	0.96	0.80	0.47	0.80
Monthly income	0.000*	0.008*	0.08	0.45
Monthly household income	0.72	0.033*	0.39	0.41
Education				
No formal education	0.36	0.59	0.58	0.99
Primary education	0.31	0.94	0.63	0.27
Universal heath scheme	0.67	0.26	0.05	0.75
Distance between the hospitals and their houses	0.45	0.34	0.30	0.29
Being member of PLHA self-help group	0.005*	0.018*	0.69	0.43
Being naïve to the ART	0.41	0.034*	0.55	0.25
Baseline CD4 cell counts	0.15	0.000*	0.000*	0.90
Baseline WHO stage IV	0.45	0.88	0.44	0.19
Initially prescribed with PI-based regimen	0.14	0.89	0.61	0.17
Type of ARV clinic				0.021*
Doctor-led	0.002*	0.000*	0.000*	0.006*
Large nurse-led	0.002*	0.57	0.33	0.11

*=Significant at p value<0.05

4.4 Survey of ART programme in Chiang Mai

4.4.1 Participants characteristics

There were 302 participants recruited in the survey part of this study; 100 from the doctor-led ARV clinic in the provincial hospital, 122 from the large nurse-led clinic and 80 from the small nurse-led clinic from the two district hospitals. Of the 302 participants, 40% were men, and 60% were women, and this pattern was consistent across all three clinics (see Table 4-35). The average age was 37 for both men and women and almost all of the participants were Buddhist. The majority of the participants had completed primary or secondary education and 40% were either married or lived with partners and nearly 36% were widow-widowers.

The majority (80.7%) of the participants received services under the universal coverage health scheme (see Table 4-35) and 60% were members of 'people who living with HIV/AIDS (PLHA)' self-help groups in their hospitals. Amongst these 302 participants, 53 were from the households with two PLHA including the participants themselves. In relation to number of children, there was about one child per household. Only six participants had HIV-infected children in their houses with five of these children being on ART.

Table 4-35: Demographic characteristics of the 302 participants

Demographic characteristics	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
N	100	122	80	302
Gender: N (%)				
Male	35 (35.0)	53 (43.4)	31 (38.8)	119 (39.4)
Female	65 (65.0)	69 (56.6)	49 (61.3)	183 (60.6)
Mean age: Years (SD)	36.1 (6.6)	38.1 (7.1)	36.9 (7.6)	37.1 (7.1)
Education: N (%)				
No formal educational	17 (17%)	40 (32.8)	25 (31.3)	82 (27.2)
Primary school	53 (53.0)	69 (56.6)	42 (52.5)	164 (54.3)
Secondary school	17 (17.0)	9 (7.4)	10 (12.5)	36 (11.9)
Higher than secondary school	13 (13.0)	4 (3.3)	3 (3.8)	20 (6.6)
Marital status: N (%)				
Single	16 (16.0)	16 (13.1)	11 (14.1)	43 (14.3)
Married or living with partner	40 (40.0)	45 (36.9)	34 (43.6)	119 (39.7)
Separated/Divorce	9 (9.0)	15 (12.3)	6 (7.7)	30 (10.0)
Widow/ widower	35 (35.0)	46 (37.7)	27 (34.6)	108 (36.0)
Type of health insurance: N (%)				
Self-pay	7 (7.1)	0	2 (2.5)	9 (3.0)
Universal coverage	66 (66.7)	110 (90.2)	67 (83.8)	243 (80.7)
Civil Servant Medical Benefit and Social security scheme	24 (24.2)	10 (8.2)	10 (12.5)	44 (14.6)
Others	2 (2.0)	2 (1.6)	1(1.3)	5 (1.7)
Status as member of the PLHA self-help group: N (%)	29 (29.0)	103 (84.4)	50 (62.5)	182 (60.3)

SD= Standard deviation; PLHA=People who living with HIV/AIDS

In relation to education, participants receiving service from the doctor-led clinic were better educated (Table 4-35); being less likely to have no formal education, and more likely to have participants with education beyond secondary school in comparison to nurse-led clinics (statistically significant, Chi-square test with $p< 0.01$).

In relation to the health insurance scheme, the doctor-led clinic received patients from either the Civil Servant Medical Benefit Scheme (CSMBS) or Social Security Scheme (SSS) (statistically significant, Chi-square test with $p< 0.01$). However, only 29% of participants from that clinic were members of PLHA self-help group compared to 84% and 62% of participants from the large and small nurse-led clinics respectively (statistically significant, 3x2 Chi-square test with $p< 0.01$). Despite the universal health access to ART provided by the government, nine participants (3%, n=301) had to pay for the treatment as they had initiated treatment before the nationwide expansion of the service.

4.4.2 Socioeconomic status

More than half of the participants (58.5%) were the main wage earner for their families, although 34% of these main wage earners had no formal education with 62% of them working as general labourers. These characteristics were consistent across the three clinics. About half (55.0%) of the participants lived in other people's houses, including their parents' houses while 40% of them owned houses. Only one participant reported no permanent residence.

The average monthly income and monthly household income of the participants were THB 4,417 and THB 5,972 respectively (see Table 4-36), however, five participants (1.6%) earned less than THB 830 per month which was Thailand's official poverty line for the Northern region of Thailand in 2004 (NESDB 2004). 28 participants reported themselves as being unemployed; most of whom were male (57%), had primary education (67%) and were under the universal coverage health scheme (85%). In terms of both monthly income and monthly household income, participants from the doctor-led clinic were richer compared to those from the two nurse-led clinics (statistically significant ANOVA test with $p< 0.01$).

Table 4-36: Socio-economic characteristics of the participants

Socio-economic characteristics	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
N	100	122	80	302
Main occupation: N (%)				
Unemployed	12 (12.0)	10 (8.2)	6 (7.5)	28 (9.3)
Farmer or gardener	6 (6.0)	8 (6.6)	8 (10.0)	22 (7.3)
Self-employed	14 (14.0)	14 (11.5)	11 (13.8)	39 (12.9)
General labourer	60 (60.0)	84 (68.9)	44 (55.0)	188 (62.3)
Housewife	8 (8.0)	6 (4.9)	11 (13.8)	25 (8.3)
Main wage earner: N (%)				
Yes	61 (61.6)	77 (63.1)	39 (48.8)	177 (58.8)
Mean income per month: THB 1,000 (SD)	6.0 (5.9)	3.4 (2.6)	4.1 (2.0)	4.4 (4.0)
Mean of household income per month : THB 1,000 (SD)	7.8 (6.6)	4.5 (3.9)	6.0 (3.6)	6.0 (5.1)
Present accommodation: N (%)				
Own occupied	40 (40.0)	51 (41.8)	28 (35.0)	119 (39.4)
Rented house/room	8 (8.0)	4 (3.3)	4 (5.0)	16 (5.3)
Live with others	52 (52.0)	66 (54.1)	48 (60.0)	166 (55.0)
Vagabond	0	1 (0.8)	0	1 (0.3)

SD=Standard deviation

4.4.3 Service utilization

4.4.3.1 Access to the clinics

Regarding mode of transport, motorcycles were the main options for 70% of participants (see Table 4-37). The average distance from home to clinic was 15 kilometres with an average travelling time of 39 minutes. However, one patient lived in another province about 450 kilometres away from the clinic, having refused to receive treatment from an ARV clinic closer to home.

Table 4-37: Participants' behaviour for ARV clinic visiting

ARV clinic visiting	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
N	100	122	80	302
Usual method used to come to the hospitals: N (%)				
By bicycle	4 (4.0)	7 (5.7)	1 (1.3)	12 (4.0)
By motorcycle	50 (50.0)	96 (78.7)	67 (83.8)	213 (70.5)
By private car	18 (18.0)	10 (8.2)	7 (8.8)	35 (11.6)
By bus/coach	28 (28.0)	7 (5.7)	4 (5.0)	39 (12.9)
Others	0	2 (1.6)	1 (1.3)	3 (1.0)
Mean of distance to the hospital: kilometres (SD)	25.5 (50.8)	8.8 (7.0)	11.4 (16.5)	15.0 (31.6)
Mean of time spent to come to hospital: Minutes (SD)	35.7 (39.5)	21.9 (12.2)	24.0 (26.9)	27.0 (28.3)

SD=Standard deviation

Both distances and travelling times to the doctor-led clinic were significantly further and longer compared to the other two clinics (statistically significant, ANOVA test p=0.001). This led to differences between participants' means of travelling to the clinics with participants from doctor-led clinics being more likely to travel by bus/coach and less likely to travel by motorcycle (statistically significant, Chi-square test p=0.001).

4.4.3.2 Time spent at the ARV clinic

The mean time spent at the ARV clinic was 2.5 hours (see Table 4-38), with a time with the doctor of 7.6 minutes and only one half of patients seeing doctors on their last visit.

Table 4-38: Time spent at the ARV clinic of the participants

Time spent at the ARV clinic	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
N	100	122	80	302
Mean of time spent at the ARV clinic: Hours (SD)	3.6 (0.9)	2.5 (1.1)	1.1 (0.5)	2.5 (1.3)
Mean of time spent at with doctors at the clinic: Minutes (SD)	7.4 (4.5)	8.6 (3.9)	6.1 (4.2)	7.6 (4.3)
Saw doctor at the last visit: N (%)	84 (84.0)	44 (36.1)	25 (31.6)	153 (50.8)
Attitude toward time spent at the ARV clinic; N (%)				
Too short	0	1 (0.8)	1 (1.3)	2 (0.7)
Appropriate	51 (51.0)	74 (60.7)	72 (90.0)	197 (65.2)
Too long	49 (49.0)	47 (38.5)	7 (8.8)	103 (34.1)
Attitude toward time spent with doctor; N (%)				
Too short	8 (8.2)	15 (12.3)	11 (14.5)	34 (11.5)
Appropriate	90 (91.8)	106 (86.9)	65 (85.5)	261 (88.2)
Too long	0	1 (0.8)	0	1 (0.3)

SD=Standard deviation; ARV=antiretroviral

For the nurse-led clinics, HIV-infected cases were looked after primarily by nurses with only the complicated cases being handed over to doctors. Only one third of participants from nurse-led clinics saw doctors for the last visit compared to 84% from doctor-led clinics (statistically significant, Chi-square test p=0.001). There was no significant difference in consultation time with doctors in both types of clinic.

The average time spent at the ARV clinic (statistically significant, ANOVA test p=0.001) was shorter in the small nurse-led clinic than either the large nurse-led or the doctor-led

clinic. Half of the participants from the doctor-led clinic reported that they had experienced too long waiting times.

4.4.3.3 Hospital appointment and HIV education

In relation to the hospital appointments, the mean interval between follow-up* was 1.2 months. Twelve participants (4.0%) reported that they had missed at least one appointment in the past three months (Table 4-39) of which six immediately visited the hospital when they realised their missed appointment.

Table 4-39: Hospital appointment and ART education

Behaviour of service utilization	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
N	100	122	80	302
Mean of follow-up duration: Months (SD)	1.8 (0.7)	1.0 (0.2)	1.0 (0.2)	1.2 (0.6)
Miss hospital appointment in the past 3 months; N (%)	6 (6.1)	2 (1.6)	4 (5.0)	12 (4.0)
Inform benefit and harm of ART; N (%)	89 (89.0)	120 (98.4)	78 (97.5)	287 (95.0)
Level of understanding in case benefit and harm were informed; N (%)				
Not at all	0	0	0	0
Partly understood	28 (31.5)	31 (25.8)	20 (26.0)	79 (27.6)
Fully understood	61 (68.5)	89 (74.2)	57 (74.0)	207 (72.4)
First consultant if had problem; N (%)				
Hospital staff	27 (61.4)	50 (51.5)	30 (61.2)	107 (56.3)
Family member	8 (18.2)	12 (12.4)	12 (24.5)	32 (16.8)
Other PLHA	2 (4.5)	13 (13.4)	6 (12.2)	21 (11.1)
NGO	1 (2.3)	0	0	1 (0.5)
Others	6 (13.6)	22 (22.7)	1 (2.0)	29 (15.3)

SD=Standard deviation; PLHA=People who living with HIV/AIDS; NGO=Non-government organisation

The follow-up duration based on the last hospital visit were also significantly different between the three clinics (statistically significant, ANOVA test p=0.001); being 1.8-months in the doctor-led clinic and approximately one-month for the nurse-led clinics, in comparison to the national ART programme guideline of one month follow-up. The longer duration of follow-up in the doctor-led clinic might be due to the greater number of patients being treated by a limited number of doctors.

* Information regarding hospital follow-up duration was from hospital records

Regarding health education about ART, 15 participants (5.0%) reported never having been informed about the benefit and risks of antiretroviral therapy. In case where information was provided, 72% of participants reported fully understanding the information provided. When the participants had any questions regarding ART, only 56% consulted hospital staff with the remainder preferring to consult with family members or other PLHA.

The participants from the doctor-led clinic were less likely to be informed about the benefits and risks of ART (statistically significant, Chi-square test p=0.003) with no significant difference in level of understanding among the participants from the three hospitals (see Table 4-39). Participants from nurse-led clinics were less likely to consult hospital staff for problems related to ART (statistically significant, Chi-square test p=0.018).

4.4.4 HIV clinical information

Three quarter of the participants discovered their HIV status through their own or their spouses/sex partners being requested to test for HIV while receiving medical treatment and being suspected of HIV infection (Table 4-40). The mean time since HIV diagnosis was approximately 5.2 years and the average duration of treatment was 11.8 months.

Table 4-40: HIV clinical information of the participants in the three clinics

HIV clinical information	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
N	100	122	80	302
Reason for HIV testing; N (%)				
During you/spouse having medical treatment	70 (70.0)	89 (73.0)	69 (86.3)	228 (75.5)
Premarital testing	4 (4.0)	4 (3.3)	0	8 (2.6)
ANC testing	13 (13.0)	10 (8.2)	8 (10.0)	31 (10.3)
Voluntary testing	5 (5.0)	5 (4.1)	1 (1.3)	11 (3.6)
For job application	5 (5.0)	0	0	5 (1.7)
For blood donation	2 (2.0)	4 (3.3)	1 (1.3)	7 (2.3)
Others	1 (1.0)	10 (8.2)	1 (1.3)	12 (4.0)
History of previous ART; N (%)	23 (23.0)	40 (32.8)	10 (12.7)	73 (24.3)
Mean time since HIV diagnosis: Years (SD)	5.1 (3.9)	5.7 (3.8)	4.8 (3.4)	5.2 (3.7)
Mean of duration of ART: Months (SD)	12.9 (11.8)	10.9 (9.8)	11.8 (9.9)	11.8 (10.5)
ART regimen used: N (%)				
First line regimen ;GPO-Vir (d4T+3TC+NVP)	89 (89.0)	97 (79.5)	72 (90.0)	257 (85.4)
Second line regimen; (d4T+3TC+EFV)	3 (3.0)	10 (8.2)	0	13 (4.3)
Third line regimen; (d4T+3TC+IDV+RTV)	2 (2.0)	1 (0.8)	0	3 (1.0)
Others regimen	6 (6.0)	14 (11.5)	8 (10.0)	28 (9.3)
Median of baseline CD4 cell counts: cell/μL (IQR)	98 (23-220)	94 (32-186)	55 (29-141)	98 (23-220)
Mean of baseline body weight: Kilograms (SD)	52.5 (9.8)	52.0 (9.4)	51.0 (9.8)	51.8 (9.6)

SD=Standard deviation; GPO=Government Pharmaceutical Organisation; d4T=Stavudine; 3TC=Lamivudine; NVP=Nevirapine; EFV=Efavirenz; IDV=Indinavir; RTV=Ritonavir

Regarding history of previous treatment, only 24% of participants reported having previous ART (Table 4-40). This emphasized the programme flexibility as the government ART guidelines stated that only naïve individuals should be eligible for the programme.

It was found that the large nurse-led clinic had more participants with a history of previous ART before entering into the government ART programme (statistically significant, Chi-square test $p< 0.01$) (Table 4-40). Participants with a history of previous treatment were generally female (64.4%) with an average age of 38 years. Their average duration on ART was 8.3 months which is shorter than those who are treatment naive*. About 60% of them

* Time was counted since entering the government ART programme, duration on previous treatment was not taken into account

were members of the PLHA self-help group and nearly half of them (49%) had initial CD4 cell counts higher than 200/μL.

No difference in socioeconomic status was detected between those naive to treatment and those previously treated; gender, age, education, monthly income and status as a member of PLHA self-help group were also similar between the two groups. However, participants with history of previous treated with ART tended to have higher of initial CD4 cell counts (mean =227 /μL) compared to participants new to the treatment (mean =96 /μL) (statistically significant, t-test $p< 0.01$).

4.4.4.1 ART regimen

According to government ART programme guidelines, three antiretroviral regimens are available to prescribe; GPO-Vir as the first line and the other two as alternative first-line therapies (see Table 4-40). Nearly all of the patients thus received medication in accordance with the guideline and, as such, a similar regimen was used in all three hospitals. However, 28 patients were treated using regimens not recommended in the guideline, with 3 of these patients having previously received ART. In all cases, regimens were prescribed according to the physician experiences and tailored to the needs of individual patients concerning effectiveness, adverse effects and toxicity or the regimen.

4.4.4.2 CD4 cell counts

The average initial CD4 cell counts of participants were 128 /μL (see Table 4-41). The majority of participants (79.6%) had initial CD4 cell counts less than 200 /μL and this was similar across the three clinics. Amongst these, six participants had 0 /μL CD4 cell counts just before starting ART, while nine participants had CD4 cell counts greater than 500 /μL upon entering the programme. The participants from small nurse-led clinic had the lowest initial CD4 cell counts; however, this difference was not statistically significant.

Table 4-41: CD4 cell counts and body weight of the participants

Variable	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
CD4 cell counts: /μL				
Median at baseline (IQR)	98 (23-220)	94 (32-186)	55 (29-141)	79 (27-171)
Median at 6-month (IQR)	169 (124-296)	152 (87-253)	159 (113-259)	157 (108-258)
Median at 12-month (IQR)	175 (151-265)	153 (92-220)	126 (112-237)	155 (101-228)
Body weight: Kg				
Mean at baseline (SD)	52.5 (9.8)	52.0 (9.4)	51.0 (9.8)	51.8 (9.6)
Mean of at 6-month (SD)	54.8 (10.5)	54.7 (9.0)	55.6 (10.2)	55.0 (9.6)
Mean at 12-month (SD)	55.9 (11.0)	55.2 (7.6)	51.5 (6.8)	54.7 (8.4)

SD=standard deviation; IQR=Inter-quartile range

When comparing CD4 cell counts after 6-month and 12-months of treatment, the CD4 cell counts increased over time (Table 4-41). Levels of CD4 cell counts at 6-month and 12-month of treatment were significant higher comparing to the baseline CD4 cell counts (statistically significant, Wilcoxon Signed Ranks test, p=0.001). In addition, CD4 cell counts after 12-months of treatment were also significantly higher than that at 6-months in participants from doctor-led and large nurse-led clinics. However, CD4 cell counts in small nurse-led clinics went down (Wilcoxon Signed Rank test, p=0.043). The increase in CD4 cell counts at 12-month compared with at 6-months did not achieve clinical significance.

4.4.4.3 Body weight gain

The average initial body weight of participants was 51.8 kilograms (Table 4-42) with half of the participants weighing less than 50 kilograms before the treatment. Similar to the CD4 cell counts, when comparing body weight after 6-months and 12-months of treatment, the participants tended to gain body weight over time except the participants from the small-nurse clinics whose body weight reduced slightly between 6 months and 12-months of treatment. Overall, body weight at 6-months and 12-months of treatment was significant higher compared to the initial body weight (statistically significant, paired t-test, p=0.001). Moreover, participants' body weight at 12-months of treatment was also significantly higher than that at 6-month of treatment (paired t-test, p=0.001). Unlike CD4 cell counts, only 27.6% of participants at 6-month of treatment and 44.6% at 12-month of treatment presented a gain in body weight ≥10% compared to baseline. The pattern of response of

participants' body weight appeared to be similar across the three clinics with no statistically significant differences being identified between the three treatment providers.

4.4.5 Self-reported adherence

Strict adherence to antiretroviral therapy is one of the most important factors in achieving a good therapeutic result (Paterson, Swindells et al. 2000); (Read, Mijch et al. 2003) with adherence levels being required of at least 95% to attain the best outcome from treatment. Adherence of each individual was summarized as the ratio between the number of taken doses and the total number of doses of all ARV drugs prescribed. However, in addition, participants were asked to recall the number of missed doses or doses that they took more than 30 minutes after the usual time in the past 5 days and in the previous month. In terms of missed doses in the past five days, 93.4% of participants reported taking all doses of ARV drugs (Table 4-43). In terms of missed doses in the previous month, 87.4% reported taking all doses of ARV drugs.

Table 4-42: Behaviour of antiretroviral drugs taking of the participants

Doses of ARV drug taking	Doctor-led clinic	Large nurse-led clinic	Small nurse-led clinic	Total
N	100	122	80	302
In the past 5 days that				
Missed doses: N (%)				
Taken all doses	87 (87.0)	118 (96.7)	77 (96.3)	282 (93.4)
1-2 doses	9 (9.0)	4 (3.3)	2 (2.5)	15 (5.0)
≥ 3 doses	4 (4.0)	0	1 (1.3)	5 (1.7)
Missed or taken later than 30 minutes: N (%)				
Taken all doses	65 (65.0)	103 (84.4)	65 (81.3)	233 (77.2)
1-2 doses	24 (24.0)	17 (13.9)	13 (16.3)	54 (17.9)
≥ 3 doses	11 (11.0)	2 (1.6)	2 (2.5)	15 (5.0)
In the previous month that				
Missed doses: N (%)				
Taken all doses	81 (81.0)	111 (91.0)	72 (90.0)	264 (87.4)
1-3 doses	16 (16.0)	9 (7.4)	7 (8.8)	32 (10.6)
4-12 doses	2 (2.0)	2 (1.6)	0	4 (1.3)
≥ 13 doses	1 (1.0)	0	1 (1.3)	2 (0.7)
Missed or taken later than 30 minutes: N (%)				
Taken all doses	62 (62.0)	98 (80.3)	62 (77.5)	222 (73.5)
1-3 doses	31 (31.0)	19 (15.6)	17 (21.3)	67 (22.2)
4-12 doses	6 (6.0)	5 (4.1)	0	11 (3.6)
≥ 13 doses	1 (1.0)	0	1 (1.3)	2 (0.7)
Adherence ≥ 95% in the past 5 days*	87 (87.0)	118 (96.7)	77 (96.3)	282 (93.4)
Adherence ≥ 95% in the previous month*	97 (97.0)	120 (98.4)	79 (98.8)	296 (98.0)

* Accounted for missed doses only (doses that patients did not take); ARV=Antiretroviral

One participant from the doctor-led clinic reported missing all doses of the antiretroviral drug, both in the past 5 days and in the previous month as a consequence of moving to another province and thus being unable to visit the clinic after the medication ran out. Another participant from the small nurse-led clinic reported missing all doses of the antiretroviral drug in the past five days and 24 doses in the previous month. He stated that such poor compliance was due to the intolerable adverse effect of the ART. Furthermore, two participants from the large nurse-led clinic stated that their medication was interrupted due to running out of the medication in the clinic. This might suggest poor logistical management in the large nurse-led clinic.

One fifth of participants (n=302) reported missing doses of antiretroviral drugs at least once since entering the programme, with 70% of this group having missed a dose in the previous

month prior to the interviews. The reason for such missed doses was mainly simply as a result of forgetting to take the medication (58.3%, n=60).

A multivariate analysis was performed to identify factors that predicted reported adherence < 95% (see Table 4-43). The analysis found that there appeared to be no association between reported adherence <95% and participants' gender, age, education, ART regimen, type of ARV clinic, baseline CD4 cell counts, baseline body weight, time since HIV diagnosis or duration of ART. The correspondence between adherence in the past 5 days and in the previous month showed a strong association between reported adherence over both time periods.

Table 4-43: Multivariate analysis of factor predicting reported adherence < 95% in the past 5 days

Predictor	OR	95% CI	P value
Gender			
Male	2.27	0.41-12.52	0.34
Female		Reference	
Age: Years	0.99	0.86-1.14	0.86
Time since HIV diagnosis: Years	1.21	0.99-1.47	0.06
Duration on ART: Months	0.99	0.94-1.05	0.83
Initial CD4 cell counts: Cell/μL	0.99	0.98-1.00	0.12
Initial body weight: Kilograms	0.98	0.90-1.07	0.63
Type of ARV clinic			0.25
Doctor-led	3.23	0.52-19.98	0.21
Large nurse-led	0.83	0.09-7.65	0.87
Small nurse-led		Reference	
History of adverse effects during treatment			0.14
No	3.29	0.29-36.60	0.33
Yes, but was able to do some work	0.36	0.02-6.91	0.50
Yes, was unable to work at all		Reference	
Highest education			0.50
No formal education	0.54	0.02-13.85	0.71
Primary school	0.70	0.06-8.52	0.78
Secondary school	2.54	0.19-33.86	0.48
Higher than secondary school		Reference	

Note. OR = odds ratio; CI=confidence interval, *P < .05.

Table 4-44: Correlation coefficients (R) of reported adherence response to different definition and time frame

Correlation	B	C	D
Number of missed doses during the past five days (A)	0.76**	0.86**	0.85**
Number of doses that missed or took later than 30 minutes in the past five days (B)	-	0.63**	0.77**
Number of missed doses in the previous month (C)	-	-	0.97**
Number of doses that missed or took later than 30 minutes in the previous month (D)	-	-	-

** Correlation is significant at the 0.01 level (2-tailed)

4.4.6 Wellbeing of participants

Prior to initiation on ART, 28.1% of participants reported being unable to work while 32.8% said that they could work normally (see Table 4-45). After taking the ART, more than 70% of participants reported improvements in terms of either their ability to work, skin, everyday activities or mental health. However, 3.6% stated that they had less ability to work, and 26.5% noticed no difference in their ability to work after taking ART. Approximately half of participants reported better health condition in all four aspects (ability to work, skin condition, daily activities and mental health) compared to before entering the treatment programme. The nurse-led clinics had more participants who reported having better health conditions in all four aspects (statistically significant, Chi-square test, p=0.001)

Table 4-45: Well being of the participants

Well being	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
N	100	122	80	302
Before entering the programme				
Not able to do work at all	22 (22.0)	42 (34.4)	21 (26.3)	85 (28.1)
Able to work as usual	34 (34.0)	51 (41.8)	33 (41.3)	118 (39.1)
Able to work normally	44 (44.0)	29 (23.8)	26 (32.5)	99 (32.8)
Ability to work comparing to that before entering the programme				
Able to do work less	6 (6.0)	2 (1.6)	3 (3.8)	11 (3.6)
No difference	38 (38.0)	20 (16.4)	22 (27.5)	80 (26.5)
Able to do work more	56 (56.0)	100 (82.0)	55 (68.8)	211 (69.9)
Skin condition comparing to that before entering the programme				
Worse	4 (4.0)	1 (0.8)	3 (3.8)	8 (2.6)
No difference	27 (27.0)	12 (9.8)	12 (15.0)	51 (16.9)
Better	69 (69.0)	109 (89.3)	65 (81.3)	243 (80.5)
Daily activities e.g. take a bath comparing to that before entering the programme				
Worse	1 (1.0)	1 (0.8)	3 (3.8)	5 (1.7)
No difference	39 (39.0)	19 (15.6)	15 (18.8)	73 (24.3)
Better	60 (60.0)	102 (83.6)	62 (77.5)	224 (74.2)
Mental health comparing to that before entering the programme				
Worse	2 (2.0)	2 (1.6)	2 (2.5)	6 (2.0)
No difference	24 (24.0)	10 (8.2)	8 (10.0)	42 (13.9)
Better	74 (74.0)	110 (90.2)	70 (87.5)	254 (84.1)
Better heath condition in all four aspect	28 (28.0)	89 (73.0)	44 (55.0)	161 (53.3)

4.4.7 ART-related adverse events

In relation to the adverse effects of ART, nearly 200 participants reported experiences of side effects from ART treatment (Table 4-46). Of this number, 59 participants were unable to work and had to stop undertaking activities because of adverse effects and ten participants stopped taking the medicines as a consequence of adverse events. Further analysis to analyse the relationship between regimen and side effects found that the adverse effects reported by participants were significantly related to the regimen used (Chi-square test, p=0.018). The analysis suggested that participants who were on a regimen containing efavirenz experienced more adverse effects than participants on other regimens. In 13 patients treated with efavirenz, 12 of them reported side effects. This result supported the findings of a national survey (MOPH 2004) which found that participants with regimens

other than GPO-Vir (first-line regimen) tended to experience more adverse effects than those who prescribed with GPO-Vir.

Table 4-46: Experience of adverse events

Adverse events	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
N	100	122	80	302
Experience of adverse effects				
No	55 (55.0)	22 (18.2)	30 (37.5)	107 (35.5)
Yes (minor effect)	36 (36.0)	59 (48.8)	40 (50.0)	135 (44.9)
Yes (unable to do anything)	9 (9.0)	40 (33.1)	10 (12.5)	59 (19.6)
Stop taking medicine if had side effect	3 (6.8)	5 (5.1)	2 (4.0)	10 (5.2)

4.4.8 Stigmatization

The majority (90%) of participants informed their partners and their families (Table 4-47) of their HIV status. However, in the case of 20% of participants, their HIV status was unknown to their communities. This is the role of the PLHA group which provides voluntary social and moral support for their members' public disclosure of their HIV status within their community. Participants from the doctor-led clinic (38%) tended to be less willing to disclose their status to their communities (statistically significant, Chi-square test, p=0.001). Of the participants who experienced stigmatization, 66% of them reported that they were more accepted after taking ART.

Table 4-47: Participants' experiences of stigmatization

Stigmatization	Doctor-led clinic: N (%)	Large nurse-led clinic: N (%)	Small nurse-led clinic: N (%)	Total: N (%)
N	100	122	80	302
Inform status of HIV infected to couple or sex partner	69 (69.0)	91 (89.2)	54 (90.0)	214 (89.9)
Inform status of HIV infected to family	86 (86.0)	117 (95.9)	77 (96.3)	280 (92.7)
Inform status of HIV infected to community	62 (62.0)	111 (91.0)	72 (90.0)	245 (81.1)
Experience of people turn away				
Never	54 (55.7)	77 (63.1)	37 (46.8)	168 (56.4)
Yes	16 (16.5)	27 (22.1)	23 (29.1)	66 (22.1)
Not sure	16 (16.5)	11 (9.0)	14 (17.7)	41 (13.8)
Neighbour and community don't know my HIV status	11 (11.3)	7 (5.7)	5 (6.3)	23 (7.7)
People accepted you more after taking ART				
Less accepted	0	0	0	0
No difference	4 (25.0)	4 (14.8)	9 (36.0)	17 (25.0)
More accepted	11 (68.8)	19 (70.4)	15 (60.0)	45 (66.2)
Not sure	1 (6.3)	4 (14.8)	1 (4.0)	6 (8.8)

4.4.9 Sexual behaviour

In relation to sexual activities, 43.1% reported having sex within the past 3 months at the time of interviews (see Table 4-48) usually with a single partner. However, four participants (0.8%) reported having sex with more than one person in the past 3 months, with one participant having four partners. Approximately 55% of participants stated that they have not indulged in sexual activities since taking ART, while five participants reported that they were more sexually active since being prescribed ART. For those who reported having sex in the previous three months, more than 80% reported always using a condom. However, five participants reported that they never used a condom which might suggest an inadequacy of counselling and health education in these cases.

Table 4-48: Participants' sexual behaviour

Sexual behaviour	N (%)
Have sex in the past 3 months	
No	169 (56.9)
Yes	128 (43.1)
N	297
Number of people have sex with in the past 3 months	
Mean (SD)	1.1 (0.3)
Range	1-4
N	126
Condom used	
Never	5 (4.0)
Sometimes	8 (6.3)
Mostly	8 (6.3)
Always	105 (83.3)
N	126
Sexual activity comparing to before entering the programme	
Less often	12 (4.0)
No difference	117 (39.0)
More often	5 (1.7)
Never had sexual intercourse since entering the programme	166 (55.3)
N	300

SD = Standard deviation

This chapter has presented the results obtained in relation to outcomes of ART delivery in Thailand and identified factors that may contribute to these outcomes. The next chapter analyses the findings in the present study in greater detail and attempts to identify factors of greatest relevance. In addition, the strengths and weaknesses of the analyses are addressed, together with the implications for policy and practice and for further research.

CHAPTER 5
DISCUSSION & CONCLUSION

5 Discussion and Conclusion

In this chapter, the findings of the present study from previous section are discussed and conclusion followed by the implications and suggestion derived from the findings. Again, the presentation in this chapter is done according the main outcomes investigated and objectives like presentation in the four previous chapters of this thesis.

5.1 Introduction

This is one of a small numbers of studies of the Thai antiretroviral therapy programme. Thailand has been recognized as being in the vanguard of scaling up ART therapy in developing country. This study of factors that contribute to those outcomes with universal access in the Thai context is longer than any other studies conducted in Thailand with an average follow up 3.7 years and examines real data rather than projections and simulation. The study included the oldest treated cases from the implementation of the programme in Northern Thailand in May 2001, preceding the official roll out of the national programme two years later. As experience of, and evidence about, ART and its outcomes are very limited in middle- and low-income countries, this study explores a national ART programme in one middle-income country where locally produced generic ART is used as first-line treatment and all eligible PLHA can enter the programme. The setting is quite specific, and as there are significant variations between countries, local research such as this is very important and is likely to be an effective way of improving practice in Thailand (Rosen, Fox et al. 2007). Moreover, determinations of factors affecting survival and ART outcomes in middle- or low-income countries are relatively rare in the literature and therefore add to the general body of knowledge (Bennett and Chanfreau 2005); (Chasombat, Lertpiriyasuwat et al. 2006); (Thanprasertsuk, Lertpiriyasuwat et al. 2006); (Lyttleton, Beesey et al. 2007); (Nunn, Fonseca et al. 2007); (Over, Revenga et al. 2007); (Rosen, Fox et al. 2007)

5.2 Antiretroviral therapy outcomes

Five hundred and one participants who initiated the treatment during March 1, 2001- April 30, 2004 were followed up for a median of 3.7 years. Seventy six cases died. More than half achieved CD4 cell counts that exceeded the level of 200 cell/uL and a quarter of them exceeded the level of 500 cell/uL. More than 31% had to change prescribed ART regimens from those initially given. Thirteen cases had disease progression with WHO staging changing either from stage II to stage IV, stage III to stage IV or stage II to stage III: many were in a very advanced stage before entering the programme. Five cases had decided to terminate the treatment themselves. Twenty-eight cases were lost follow up. Seventy five of them were referred to receive the treatment at the nearby health facilities. Approximately 20% of them experienced adverse reaction from using ART. Moreover, 24 patients were resistant to the prescribed treatment.

5.2.1 Mortality

Since the commencement of HAART in 1996, many studies have shown significant reduction of mortality and improved survival but most were limited by short follow up times. In the survival analysis of our study, 76 cases died with the mean survival of 93 months, and the main cause of death was still related to HIV/AIDS.

More than half of deaths occurred in the first year which this can be seen from the steep falling curve at the beginning of survival curve (see section 4.1.1) due to the fact that people were mostly in the advanced stage. During the follow up period in this study with mortality rate of 16%, it suggest a good comparable outcome with that from developed countries (van Sighem, Danner et al. 2005); (Kumar, Kilaru et al. 2006).

The initial phase of HAART is thought to be critical. However, two studies in Thai HIV-infected children showed that ART can be effective for children even in the advanced stage (Puthanakit, Aurpibul et al. 2007); (Puthanakit, Aurpibul et al. 2007). Moreover, the critical

period of hospitalization and death was in the first 24 weeks and the infection mostly occurred in the first three months after the initiation of ART (Manosuthi, Chaovavanich et al. 2007). Still survival analysis studies which identify the benefit of HAART in resource-limited countries, especially with long follow up time, are still limited (Badri, Bekker et al. 2004); (Fassinou, Elenga et al. 2004); (van Kooten Niekerk, Knies et al. 2006).

5.2.2 Health-related quality of life

Changes in health-related quality of life after the period of three years on HAART were examined in 97 randomly selected patients from three facilities. At the first time to examine the quality of life in 2004, the participants stated that their quality of life before the initiation of HAART were generally poor as nearly all of the participants were in advanced stage (stage III and IV). However, at the interviews in 2004 when they were averagely treated about a year, almost all of the participants in my study felt better.

In present study, the quality of life was re-evaluated again in 2007. Over the three years on HAART, the HR-QOL of the participants in the present study was unchanged. This shows the quality of life did not deteriorate over time in keeping with a previous two-year study (Saunders and Burgoyne 2002). This might be due to the fact that the evaluation was done after the induction phase which is the critical period of change in HR-QOL (Burgoyne, Rourke et al. 2004).

Another interesting finding from the present study is that, the number who reported being better off was relatively smaller than those reported being worse off in many domains used to measure quality of life of the two sets of questionnaires. This present study found that the participants required more support comparing to what they reported in 2004. This is an important dimension to explore as in one study, it was shown that the family and social support was strongly associated with HR-QOL (Jia, Uphold et al. 2005).

The findings in present study were similar to the findings in studies by Miners and Jia which stated that HR-QOL in PLHA seemed to be lower than general population (Miners, Sabin et al. 2001); (Jia, Uphold et al. 2007). It was also in agreement with most studies which show significant improvement of HR-QOL in PLHA after receiving HAART (Nieuwkerk, Gisolf et al. 2001); (Liu, Ostrow et al. 2006); (Jia, Uphold et al. 2007). My findings are also similar to the results from studies in the resource-poor environments such as Senegal, Uganda and South Africa , which found that the HR-QOL was improved by HAART using either specific measures (e.g. MOS-HIV) or generic measures (e.g. SF-36, Europol) (Jelsma, Maclean et al. 2005); (Poupard, Ngom Gueye et al. 2007); (Stangl, Wamai et al. 2007); (Philips, Zachariah et al. 2008) , One other recent Thai study of the effect of the national antiretroviral treatment programme on HR-QOL revealed that PLHA felt satisfied and contented and had courage to fight for the rights to access to HAART because of the good results of ART on their health. Health-related quality of life of those treated with ART was improved compared to those without the treatment (Chariyalertsak, Oberdorfer et al. 2006). The present study also showed that significant immunological improvement, as measured by CD4 counts in the first year after ART, occurred in the same direction as their HR-QOL. This is similar to the findings of Gill which showed that HR-QOL and CD4 cell counts were strongly associated (Gill, Griffith et al. 2002).

5.2.3 Immunological improvement

The present study only used CD4 cell counts for the monitoring of treatment and disease progression according to the guideline of national antiretroviral therapy programme in Thailand at that time, except in those suspected of treatment failure in whom samples were sent off for viral load and resistance testing. As there are still financial barriers to routine CD4 count and HIV viral load monitoring in Thailand, as well as in other developing countries, the national ART programme only uses CD4 cell counts as the main monitoring tool.

In the present study, a bit more than half and a quarter of participants could have the CD4 cell count approach the level of 200 and 500 cell/uL during the study period. Even though CD4 count at baseline and response of CD4 count are important in predicting CD4 counts less or equal 200 cell/uL (Sterling, Chaisson et al. 2003); (Kawado, Hashimoto et al. 2006); (Srasuebkul, Ungsedhapand et al. 2007), clinical and immunological measurement have a lower sensitivity than RNA viral load in determining treatment failure (Chaiwarith, Wachirakaphan et al. 2007). This suggests a considerable value of viral load in addition to the use of CD4 cell counts.

5.2.4 Duration on the first-line regimen

Approximately 85% of the participants started the treatment with the first-line regimen (GPO-vir) which is the locally produced generic ART followed the recommendation of the national ART guideline. The regimen were changed in 30% of the participants with the two main reasons were either the patients developed drug resistance or experienced adverse event. The most common side effects were lipodystrophy (nearly 50% of all adverse events)

Drug resistance is another important problem even in PLHA who naïve to the treatment. In our study, about 4.8% of the participants developed drug resistance, initially defined by a worsened clinical presentation (e.g. high viral load despite treatment, advance staging, developing new opportunistic infection) and confirmed by test for drug resistance during the period of the study. A surveillance system for drug resistance should be an essential part of the scale up of the treatment in Thailand.

Nearly one-fifth of the participants in our study experience some degree of toxicity of ART. This is in keeping with other studies from Thailand. One cohort of 417 Thai participants showed that one fourth of the patients developed grade III/IV toxicity including hepatotoxicity, dyslipidemia, hypertriglyceridaemia and anaemia (Nuesch, Srasuebkul et al. 2006). Adverse effects of the use of ARV in relation to dyslipidemia in Thai children has

been demonstrated by another study with a follow up period of approximately two years, and this was strongly associated with baseline dyslipidemia and regimen of ART (Kerr, Duncombe et al. 2007). In one recent study with fewer participants and a shorter follow up period, findings still suggested that side effects were common especially in those who prescribed protease inhibitors both single and double boosted (Hiransuthikul, Hiransuthikul et al. 2007). In group of PLHA with the non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy, lipodystrophy was also observed in half the children at the nearly three years follow up (Aurpibul, Puthanakit et al. 2007). Findings were similar in one small study of children who received HAART (Lapphra, Vanprapar et al. 2005).

5.3 Factors determining ART outcomes

In term of factors determining the outcomes, they can be divided into three categories

1. Socioeconomic factors (i.e., gender, occupation and income, type of health insurance, education)
2. Baseline clinical factors (i.e., baseline CD4 cell count-WHO staging, and history of previously treated with ART)
3. Factors associated with ART delivery (i.e., initial prescribed regimen, being member of PLHA self help group and type of ARV clinic)

In the present study, disparities of outcomes were observed and these were associated with factors mentioned above. For instance, from the Cox model, it was found that being male and people in low socioeconomic such as unemployed patients with low-income tended to die faster, moreover, their immunologic status (measured using CD4 cell counts) did not respond well to the treatment; the poorer tended to die faster. This has been described before by Mcfarland (McFarland, Chen et al. 2003). Baseline clinical factors such as CD4 cell count were also found to be highly associated with outcomes such as the rising of CD4 cell count to approach the level of 200 and 500 cell/uL; the higher CD4 cell count at baseline, the better of immunologic response to the treatment.

The method of ART delivery was also found important as the participants in doctor-led tended to survive more than those who treated in nurse-led clinics. Types of health facilities were shown to be associated with mortality and regimen changes; fewer participants from doctor-led clinic died and more participants from doctor-led clinic had their prescribed regimen changes. These findings imply influence of doctor experience over the outcomes as demonstrated before (Kitahata, Koepsell et al. 1996); (Stone, Mansourati et al. 2001); (Landon, Wilson et al. 2003). The present study emphasizes the differences of effects on outcomes in relation to mortality, immunological response and changes of prescribed ART regimens when the care was delivered by different care takers; by doctors and by nurses. For instance, the treated participants in doctor-led tended to die less and more likely to be prescribed with alternative regimens comparing to those who treated in the nurse-led clinics. This might be due to the fact that doctors deliver better care and can deal with problems arisen from the treatment better that trained nurses. Therefore, the substitution of works of the doctor by nurses or other trained health personnel may end up with trade off between quality and costs.

In context of Thailand, The existing of PLHA self help group also affected the outcome as people who were the member of the group tended to respond well with treatment (defined by the increase of CD4 cell counts) and were likely to survive compared to those who were not the member. This might be due to the rolls of group to assist PLHA to adhere to the treatment as well as to support the members throughout the course of the treatment. The findings emphasize the role of PLHA self-help group in Thailand and correspond with a previous study which explored the function of PLHA, but this was done qualitatively with no outcome measures (Lyttleton, Beesey et al. 2007). The present study setting requires cooperation with community and PLHA self-help group similar to that described by Farmer in 2001 about a community based approach to ART in rural Haiti (Farmer, Leandre et al. 2001). This was due to the shortage of health manpower which severely aggravated the

problem of poor accessibility to HAART (Muula, Chipeta et al. 2007); (Philips, Zachariah et al. 2008) and might pose unfeasible monitoring demands, drain valuable resources from more important prevention efforts (Lange and van der Waals 2002) as one study also revealed that 85 clinical officers and physicians and 91 nurses had to provide HAART to nearly 100,000 PLHA, requiring far less use of human resources than would be estimated based on the literature from other countries (Muula, Chipeta et al. 2007).

Our study does not aim to identify the factors determining accessibility to HAART. However, a cross sectional study in Khon Kaen, North eastern Thailand indicated that there were inequalities in access to and use of ARV among PLHA by health insurance status; patients who were covered by the Civil Servant Medical Benefit Scheme were significantly more likely to be prescribed with ARV than those who were covered by the universal health scheme or a publicly-funded medical insurance (Kitajima, Kobayashi et al. 2005). However, this study was based merely on secondary data of those who registered themselves at the ARV clinics without a true control group and thus, its validity could be questioned.

5.4 National antiretroviral therapy programme

The initial survey which forms the earliest part of the present study included a total of 302 participants from three ARV clinics; doctor-led, large nurse-led and small nurse-led ARV clinics in Chiang Mai, Northern Thailand. Generally, patients' characteristics and HIV clinical information were similar across the three clinics; they were middle-age, quite poor with primary education with more women than men. However, this study did note differences in term of incomes, types of health insurance, status as the member of the PLHA self-help group, level of adherence and number of patients with previous ART experience.

As the doctor-led clinic was located in the city area while the other two nurse-led clinics were sited in communities away from the city, participants who came to get services from the doctor-led clinic had to travel and spent a longer time travelling than participants from

the nurse-led clinics. This affected method of transportation to the clinics. However overall, the key characteristics of participants were generally similar to that from the national survey which conducted by the Thai MOPH previously (MOPH 2004).

When differences occurred, they tended to be due to the geographic distribution; urban versus rural area. This partially determines utilisation of different type of health facilities, urban people are more likely to go to provincial hospital (doctor-led) and people from the rural area tend to seek services from district hospital (nurse-led clinic). This delivery of services through different types of health facilities has an effect on both users' and providers' behaviours which might cause differences in treatment outcomes.

In Thailand, delivery of ART throughout the country has been done mainly via the hospitals. Thus, majority of PLHA received the treatment via the hospital based ARV clinics (Thanprasertsuk, Lertpiriyasuwat et al. 2006). However, in rural communities such as districts of Chiang Mai, Northern Thailand where we conducted this study, the treatment was mainly delivered by trained nurses, with referral to doctors in complicated cases that only half of the participants saw doctor for the last visits. Still, only limited literature describes nurse-practitioner and HAART (Gross, Bilker et al. 2002).

Over the follow up period in present study, the number of women who were prescribed ART was higher than men. This was similar to what was found in one multi-centre study to evaluate the gender and the utilization of HAART (Beusterien, Davis et al. 2008), and what has been reported by UNAIDS (UNAIDS 2008). The characteristics of the treated individuals in present study; generally poor with low education, and in advanced stages of the disease is seen in much of the literature about HIV/AIDS in developing countries (Orrell, Bangsberg et al. 2003); (Jaffar, Govender et al. 2005); (Orrell 2005); (Wolf, Davis et al. 2005); (van Kooten Niekerk, Knies et al. 2006).

In the present study, self-reported adherence was chosen as a method of measuring adherence as it is one of the most frequently used method in developing countries (Diabate, Alary et al. 2007). This is both pragmatic and valid; one meta-analysis of 65 studies has shown that self-reported adherence can distinguish between clinically meaningful patterns of medication-taking behaviour and is significantly associated with the relation between adherence and virologic response (Nieuwkerk and Oort 2005). Our cross-sectional survey showed that adherence was very high. Moreover, with the re-evaluation in 2007, their adherence to the medication did not change much over the period of three years as nearly all of them reported of having adherence above 95%. This was not unexpected as the participants who reported this were those who managed to survive over the interval of three years and to so, a high level of adherence is required.

For the high adherence in the present study, the findings are similar to one study from Bangkok, Thailand which showed that self-reported adherence using visual analogue scale was comparatively high, and this was strongly associated with undetectable viral load (Maneesriwongul, Tulathong et al. 2006). Still, this has to bear in mind that even the self-report is practical and closely related to the viral load however; cultural differences should be taken into account for interpretation of the findings. For instance, as mentioned earlier that the patients in present study valued the treatment as a hope to survive therefore they were very strict to adhere to the treatment and they also respected doctors and other care providers, they might choose to give the answer to please them.

The findings regarding adherence in present study is in agreement with many studies in African nations such as in Senegal where expansion of HAART was cautioned against due to the fear of poor compliance. It was later found that patients' compliance is not a barrier to delivery of HAART and the results from those studies shows the favourable outcome in relation to CD4 cell counts and viral suppression (Desclaux, Ciss et al. 2003); (Orrell, Bangsberg et al. 2003); (Moatti, Spire et al. 2004); (Orrell 2005). However, one has to be

aware that factors that cause poor adherence are numerous as described in one systematic review which included both qualitative and quantitative studies from both developed and developing countries. It suggested that important barriers reported in both economic settings included fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, number of pills required, decreased quality of life, work and family responsibilities, falling asleep, and access to medication. The findings from this review were consistent amongst all nations (Mills, Nachega et al. 2006).

In the evaluation in 2004, stigma regarding HIV infection in the participants was found to be decreased. Mood and stigmatization of the HIV-infected patients which are one part of HR-QOL are another two important aspects of HIV/AIDS care which have been found to be related the compliance (Alfonso, Bermbach et al. 2006); (Alfonso, Geller et al. 2006). This suggests a requirement for assessing stigma and support from the health system that delivers HAART. The findings in the present study agree with a qualitative study in Brazil which has shown that universal access to HAART can lessen stigmatization in children (Abadia-Barrero and Castro 2006). Another important assessment to be mentioned here as it is one of the important indicator for health related quality of life (Meng, Anderson et al. 2006) is that the participants have shown that they were likely to be able to return to their work after the initiation of HAART.

In 2004, in the present study, the participants' health conditions in relation to their skin condition, mentality, and physical well being improved after initiation of the ART. More than 80% of the participants reported improvement of their skin condition after initiation of HAART. However, in 2007, lipodystrophy was the commonest adverse effects among the participants, mainly in those on stavudine. This is not a surprise as this type of side effect can be caused by either NNRTI- or PI-based regimen (Steel, Landsittel et al. 2006). Thus, close monitoring for side effects is also required throughout the treatment course. The present study found that people who experienced adverse effects from ART stopped taking

the medication: this also seen in one Canadian qualitative study which showed that medication factors was the leading cause of non-adherence (Mills, Nachega et al. 2006).

Another negative consequence of HAART is the potential of the patients to resume risky behaviour such as unprotected sex (Crepaz, Hart et al. 2004). In this present study, less than half of them were still sexually active when interviewed in 2004 but the rate of using condoms was impressively high as people might be optimistic for the treatment; if people think it is effective, they also beware of risk behaviour (Huebner, Rebchook et al. 2004); (Obermeyer and Rajkumar 2004). In the present study, there were still some patients reported of not using condom during sexual intercourse which reflect the need for implementation of prevention strategies more aggressive in the risk group.

5.5 Study validity

The PLHA in this study were all from Chiang Mai, Northern Thailand where the ART programme was implemented two years prior to the official launch of the national programme in 2003. This may therefore be different to the overall picture of ART programme in Thailand. The team of staff was well trained with more financial support than usual and this may have led to better outcomes in these PLHA. The normal Thai criterion for PLHA to be entitled to ART is that the CD4 cell count should be lower than 200 cell/uL. However, our study showed that the programme also included PLHA with higher CD4 cell count than that level; this showed the flexibility of the criteria within the selected facilities. As PLHA's CD4 cell counts should be lower than 200 cell/uL to be eligible to enter the programme, the participants were mostly in an advanced stage (WHO stage III or IV) before starting treatment. The treatment outcomes in this present study may therefore be less favourable and not comparable to those found in many studies where patients are enrolled at higher CD4 cell counts (e.g. $\leq$ 500 cell/uL) (Moore, Stanton et al. 1994); (Strathdee, Palepu et al. 1998); (Cunningham, Markson et al. 2000); (Palella, Deloria-Knoll et al. 2003); (Galai, Vlahov et al. 2005); (Braitstein, Brinkhof et al. 2006). However some studies also

suggest that ART initiation could generally be delayed until the CD4 cell counts approaches 200 cell/uL (Duncombe, Kerr et al. 2005). Thus, it might still be appropriate to use that level of CD4 cell count as the cut point for inclusion criteria in the Thai programme.

In relation to the health-related quality of life of the PLHA, one must be aware that these data came only from group of PLHA who survived the three year period. The HR-QOL of these PLHA is therefore likely to be better than those who died or did not show up for the second interview. However, the aim of the study is to explore the HR-QOL after the launch of the programme and does not aim to generalise the findings beyond this fact. Evaluation of HR-QOL depends upon completion of questionnaire, the conventional approach (Wu 2000) and therefore no information can be obtained from those who died. The two sets of questionnaires used in the present study were generic and not specific to HIV/AIDS. Thus, the outcomes might be less precise. However, many studies regarding HR-QOL show that generic measures such as Euroqol and SF 36 are practical to use (Arpinelli, Visona et al. 2000); (Delate and Coons 2001); (Wu, Jacobson et al. 2002). When comparing generic and specific instruments to measure HIV/AIDS HR-QOL generic measure are more sensitive than specific measure like MOS-HIV (Wu, Jacobson et al. 2002). With differences in domain measures, the tests cannot be compare directly (Wu 2000). The questionnaire used in the present study contains some sensitive issue such as questions regarding sex. Use of the qualitative approach may help us better understand such issues.

Another important aspect to be considered in interpretation of the results is that some baseline characteristics that influence the outcomes, such as gender, are constant; however, other factors such as occupation and income could alter over the course of treatment. This may make the contribution from those factors to outcomes very difficult to interpret. One of the important aspects of the present study is that it is the combination of both prospective and retrospective cohorts. The use of the retrospective data may lead to data loss as mentioned in the method section. Attempts were made to minimise this retrieving all

possible data and trying to validate it by contacting with related health facilities and patients' families. The fact that people in this setting did not relocate much also helped to minimise lost data. Despite this, 5.6% of data was lost although this is small compared to studies in the literature which could be around 25-44% (d'Arminio Monforte, Lepri et al. 2000); (Ahdieh Grant, Silverberg et al. 2001); (Dorrucci, Pezzotti et al. 2001); (Barron, Cole et al. 2004).

5.6 Implications

One of the biggest limitations in determining the best possible choices of HAART for each individual is the shortcoming of available information from present randomized controlled trials that include both long term side effects and problems with long-term adherence (Jones and Gazzard 2006).Most studies in developing countries in present literature are conducted over period less or equal to one year (Louwagie, Bachmann et al. 2007); (Poupard, Ngom Gueye et al. 2007); (Stangl, Wamai et al. 2007). Thus, studies with longer follow up period are required; the Thai context is quite specific and ART programme in Thailand is considered as the front line for developing countries. It may be possible to generalize the key findings here to many countries with a similar situation and perspective.

5.6.1 Implications for policy and practice

HAART can be successfully initiated in people with very advanced HIV stage; low mortality was observed in this study where HAART was started in people with CD4 cell count lower than 200 cell/uL. Despite this, baseline CD4 was a strong predictor for immunological response; the higher at baseline, the better the response. At present, asymptomatic PLHA do not begin care until they are in the advanced stage (CD4 cell counts less than 200 cell/uL). Many other studies, suggest that initiation of the treatment at an earlier stage can yield higher benefit from the treatment. Thus, the proper point to start ART and the criteria at the enrolment should be rethought to suit each individual.

There should be a point to inform negative and positive consequences of HAART to make them aware and prepare for the effects of the treatment as some of the participants still do not fully understood about the consequences of HAART. This is to ensure that the patients will understand and adhere throughout this life-long treatment course as majority of them are generally poor with low education level, and the role of PLHA self-help group is important here. Moreover, the proper prevention methods for each individual who entitle into the programme should be conveyed and enhanced as what found in the present study that risk behaviour were still found.

In relation to health-related quality of life in the present study, it was found to be stable. However, many participants reported becoming worse off in terms of support over time and as this is important to maintain a high adherence level, assessment and support from the health system that initiated HAART are required.

Utilization of VCT in the Thai culture was found to be rare: 75% participants from the survey discovered their sero-status when they or their families got sick and were suspected to have HIV infection. The health system should promote the use of VCT in risk groups.

Prevention is still a mandatory strategy that should not be overlooked as some PLHA who are receiving the ART and feel healthy may want to resume an active sexual life which might increase risk of HIV spreading, Thus, effective prevention is still important and needs to convey the right message to this group of PLHA as a minority of participants in the present study reported that they still had sexual activities with no protection (do not use condom at all).

Drug-resistance is one of the expected problems after some period of implementation of the treatment programme. Moreover, monitoring and surveillance system in Thailand is still suboptimal. In order to avoid the rapid emergence of resistant viruses in a resource-poor

setting like Thailand, close surveillance of antiretroviral drug resistance should be encouraged.

As adequate human resources are a prerequisite for the success of the treatment programme, a long-term human resource plan needs to be developed. In Thailand, almost all of the treatment is delivered through hospitals; however, the trained nurses are principle carers of PLHA in the district hospitals which mostly play the major role in filling the need of the PLHA in the rural areas. Limitations of HIV/AIDS care were observed in the present study especially among complicated patients, particularly in the later years of the programme due to drug resistance and adverse effects. Empowerment of care givers should be taken into consideration as well as empowerment of the community to engage in the health system.

In the present study, disparities among groups with various backgrounds were demonstrated. Thus, assessment of disparity in term of access and benefit from HAART should be done periodically. Given the size of the programme, the existing challenge is also to create a health financing system that can ensure the fair utilization of health services and distribution of treatment benefit to different groups of people and to reach each individual in the country equally, especially people who are not covered with the universal health scheme such as migrants and ethnic minorities. Prevention and treatment are also inadequate in this population subgroup.

The ART programme should look after closely with those who in low socioeconomic due to their relatively high mortalities after the roll out of the programme, moreover, the roll of PLHA self-help group is quite important in the Thai context, strengthen and expanding the capacity of the group would enhance patients adherence which will later give the favourable outcome in both survival and immunological response

5.6.2 Implications for research

The area of HAART is rapidly changing, and the validity of findings has been compared within the contexts of other conducted studies. The main need is for knowledge which is relevant to policy and practice. For the present study, additional research would increase our insight and understanding of implementation of HAART in the Thai context. This includes:-

- Multi-centre prospective cohort study which includes more participants from various types of participants including university hospitals with longer follow up period and multiple points of assessment over a study period.
- Evaluation of the patients using disease specific such as MOS-HIV questionnaire would give quality of life information particular to HIV/AIDS, and this could be done cooperatively with qualitative approaches for more intuitive understanding.
- This study did not explore the factors determining access to HAART. However, the entry point of the treatment is also another predictor for treatment outcomes. A prospective cohort to follow up patients after their diagnosis of HIV would help to identify those who are likely to be prescribed and utilize HAART, especially in places where the criteria for the enrolment is not rigorous, and it would also help to identify the prevalence of health care providers in term of HAART prescription.

5.7 Conclusion

In the present study, 76 out of 501 cases died with the mean survival of 93 months, and the main cause of death was still related to HIV/AIDS which comparable to those found in studies from developed country. When the ART programme was rolled out, the patients responded very well in term of better quality of life and immunologic response (CD4 cell counts) during the first year when they were in the very advance stage at the baseline. However, after the induction phase, their quality of life seemed to be stable over the study period of three years. A bit more than half and a quarter of participants could have the CD4 cell count approached the level of 200 and 500 cell/uL and approximately 85% of the participants started the treatment with the first-line regimen (GPO-vir) which is the locally

produced generic ART. The regimen were changed in 30% of the participants with the two main reasons were either the patients developed drug resistance or experienced adverse event. The role of PLHA self-help group is quite impressive as it is related to relatively high survival and high immunologic response to the treatment amongst the members. Thus, their role should be expanded, strengthened and cooperated in to the ART programme.

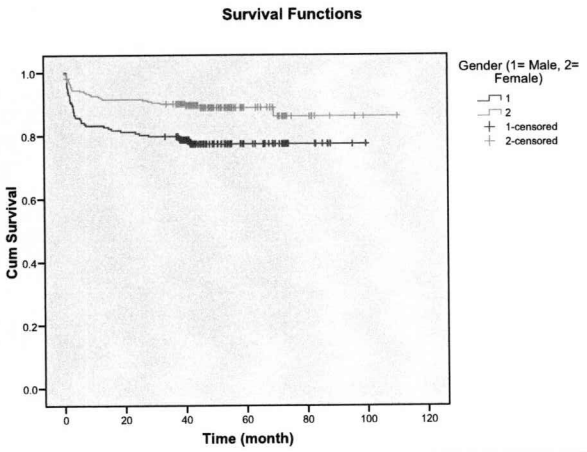
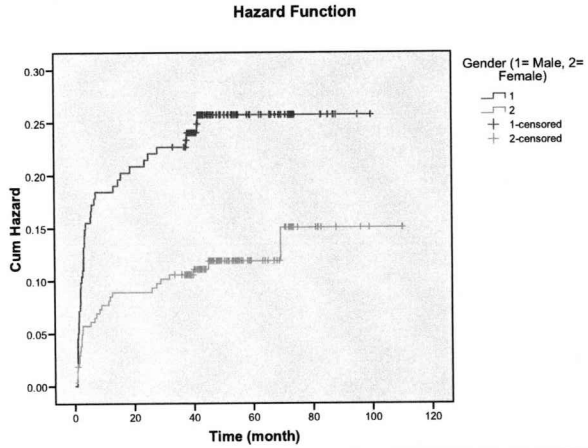
The study reveals another exemplar to ART delivery in a developing countries where most patients were poor, low educated and in advance stage of the disease. With the high volume of patients and shortage of doctors, some works of doctor has to be replaced and done by nurses especially in the rural settings. And again, as some of the doctors' works have been transfers to nurses due to the shortage of manpower, we have to bear in mind that this could end up with trade off with high mortality of the patients. The induction phase is critical, as most of the patients died and most of prescribed regimens were also adjusted during this period. Thus, the programme should look after this risk group closely. It was also found that people with low socioeconomic status had relative high mortalities and react not well to the treatment in term of immunologic response. Thus, the programme should look after carefully in this risk group. Prevention is still required and emphasized in some PLHAs as they had reported of resuming to their risky behaviours.

This study represents the first detailed study of its type aimed at evaluating the role of socioeconomic factors in determining the outcome of antiretroviral therapy in Thailand. Given its innovative nature, a number of strengths and weaknesses underlying the study are acknowledged. My hope is that the strengths of this study can generate sufficient interest to ensure that follow-on research facilitates the correction of these weaknesses.

6 Annexes

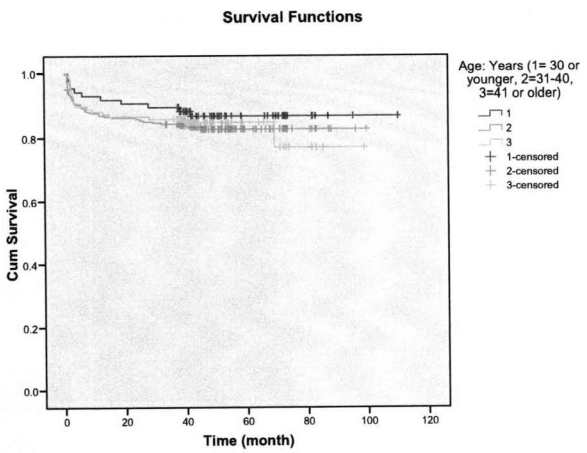
6.1 Annex 1: Log rank test for four treatment outcomes

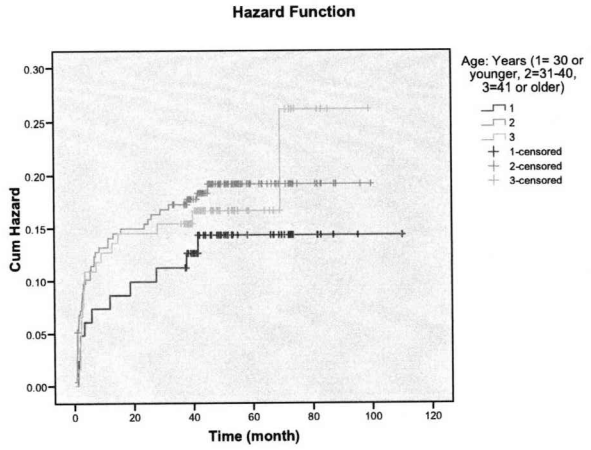
Table 6-1: Log rank test for potential predictors of mortality

Predictor	Survival function	Hazard function	P-value
Gender			0.001*

Age: Year

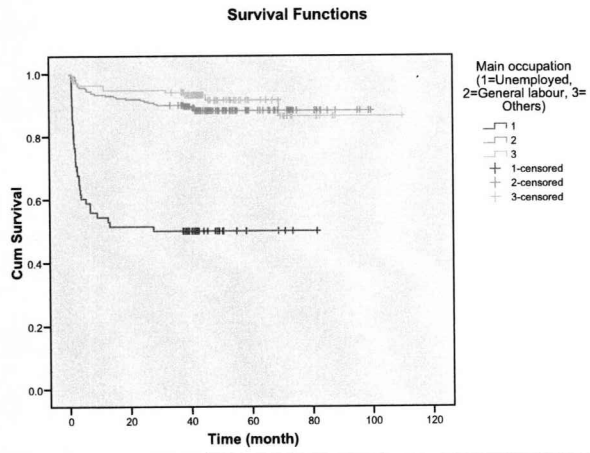
0.64

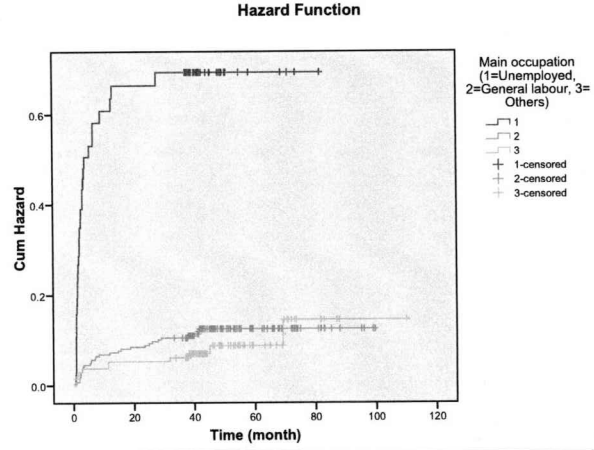




Main occupation

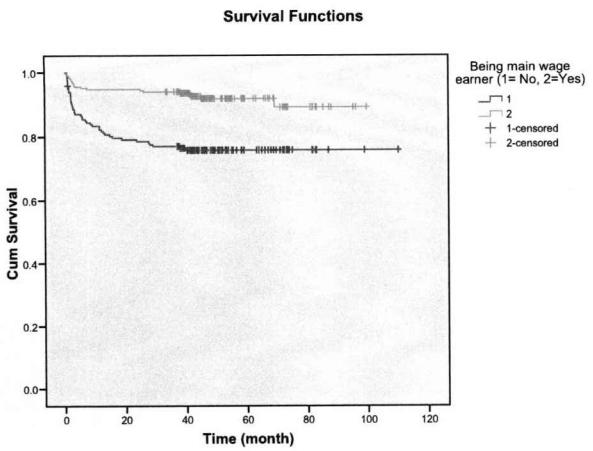
0.000*

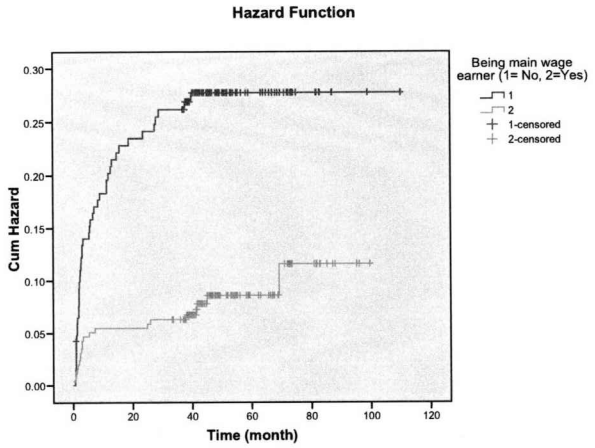




Being Main wage earner

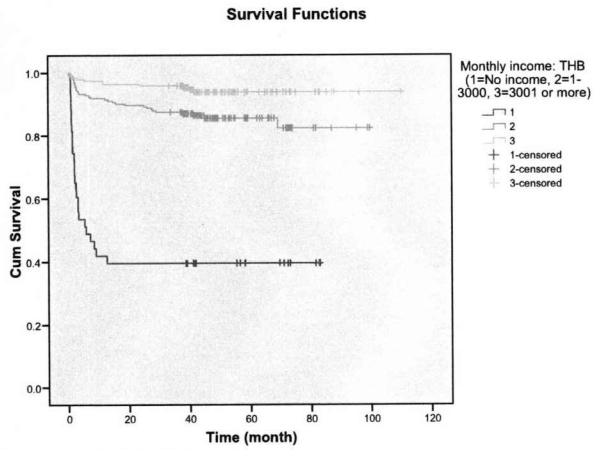
0.000*

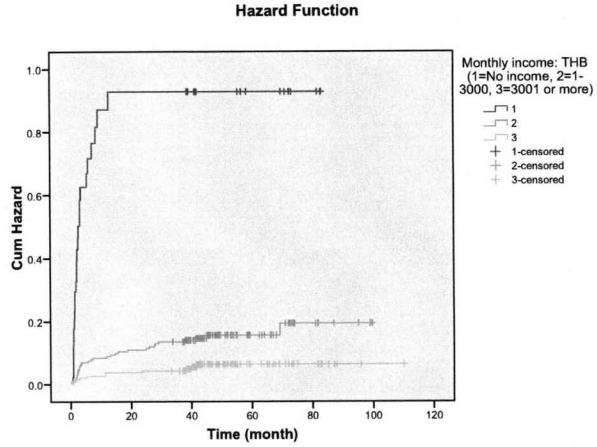




Monthly income: THB

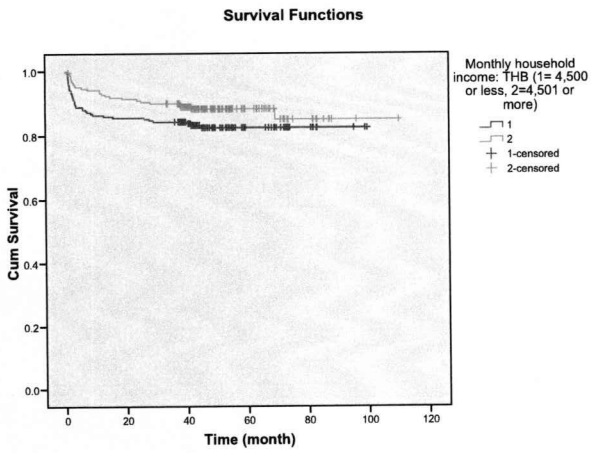
0.000*

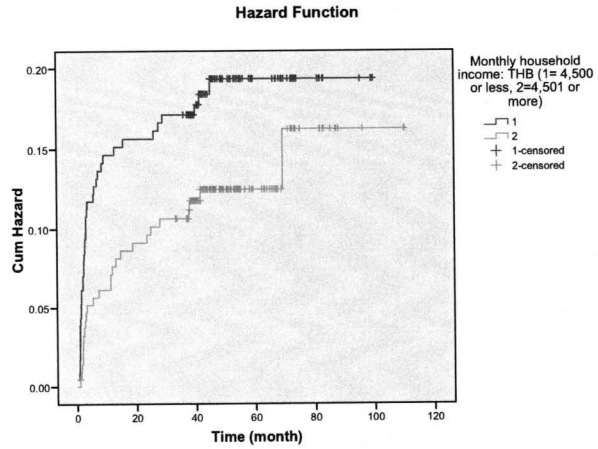




Monthly household income: THB

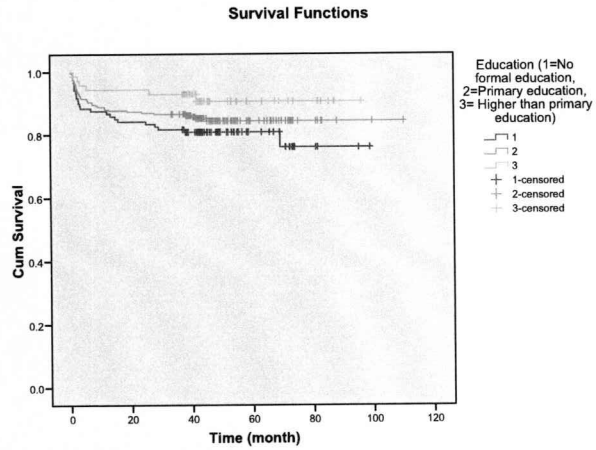
0.11

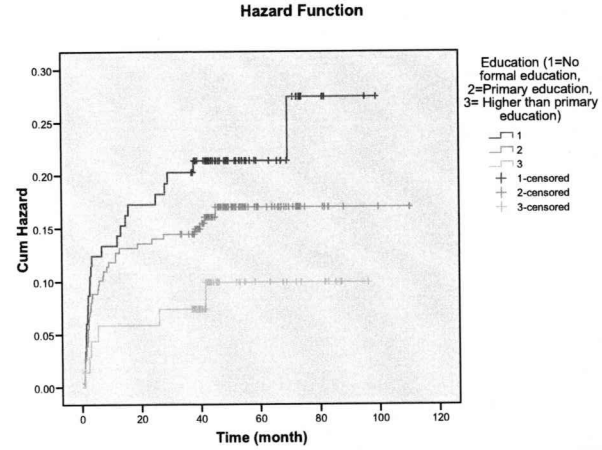




Education

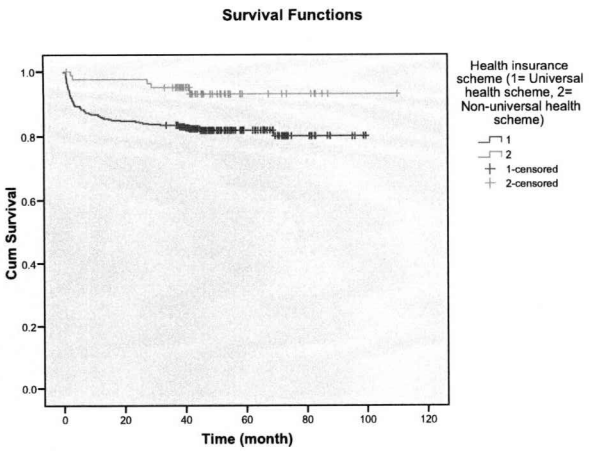
0.12

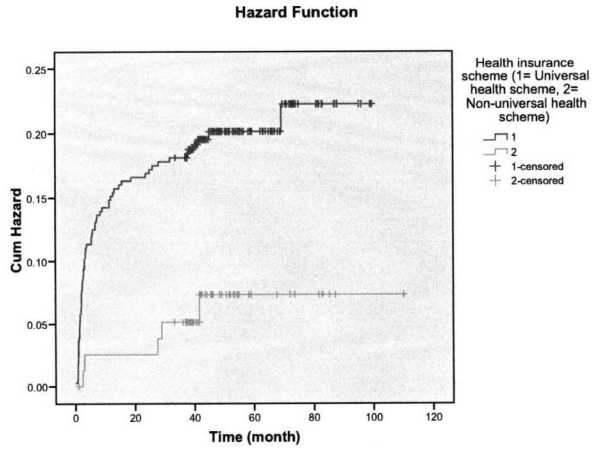




Health insurance scheme

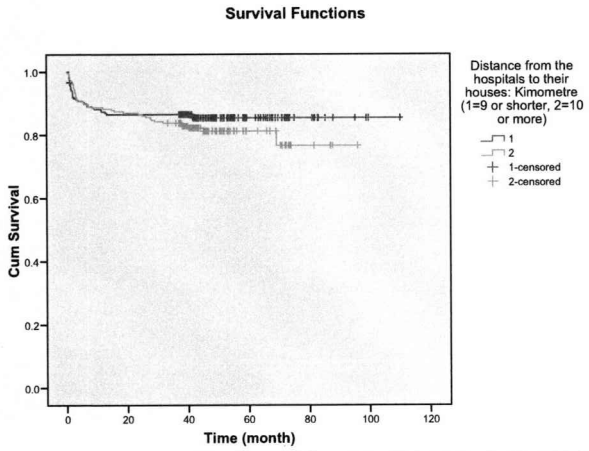
0.01*

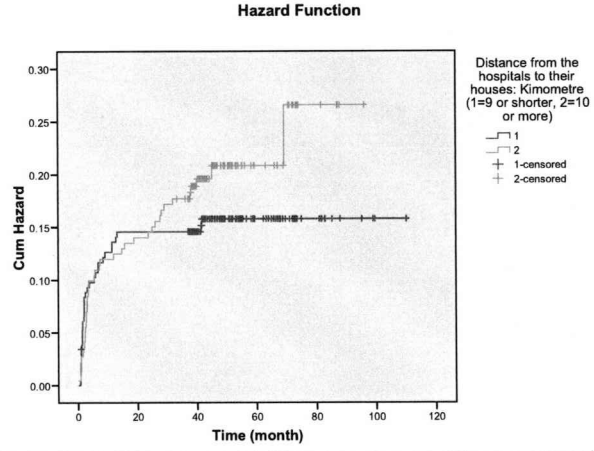


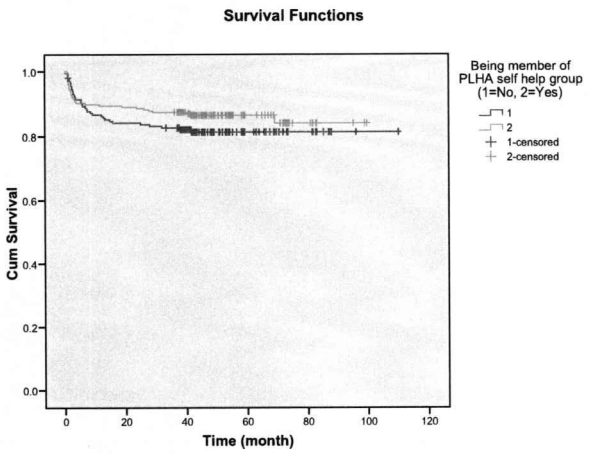
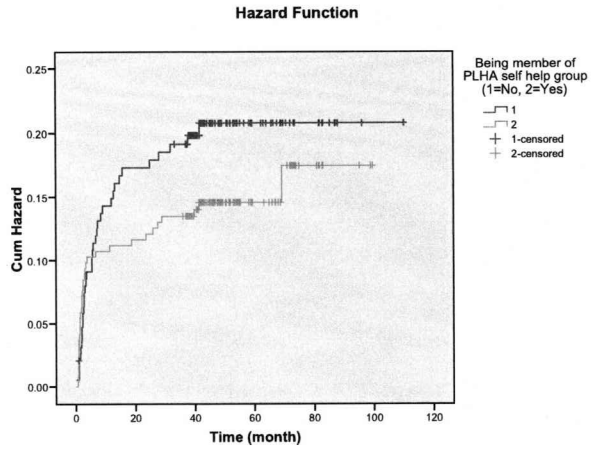
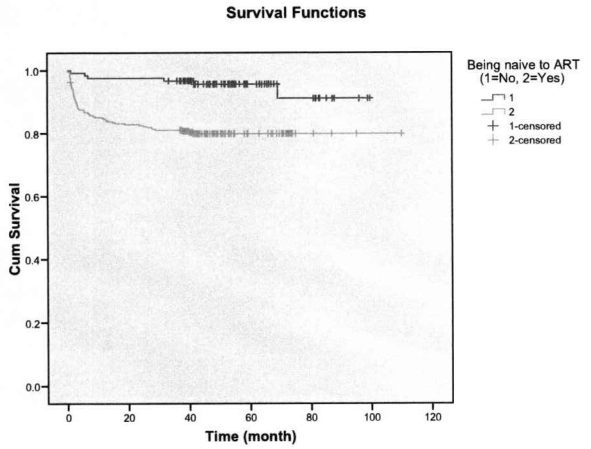
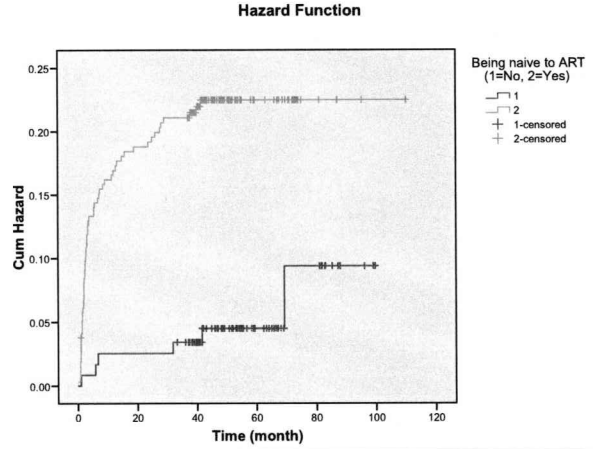


Distance between hospitals and their houses: Kimometre

0.26

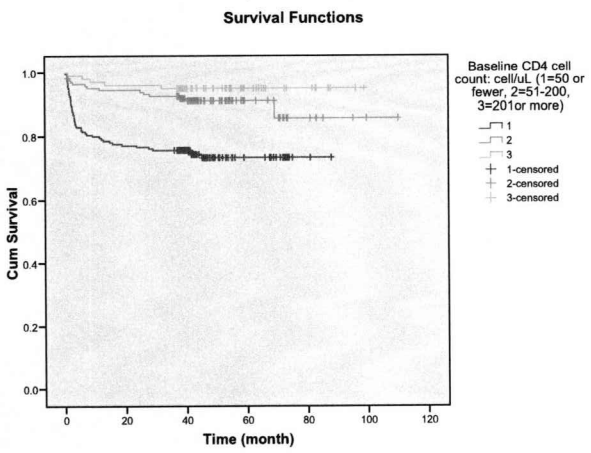


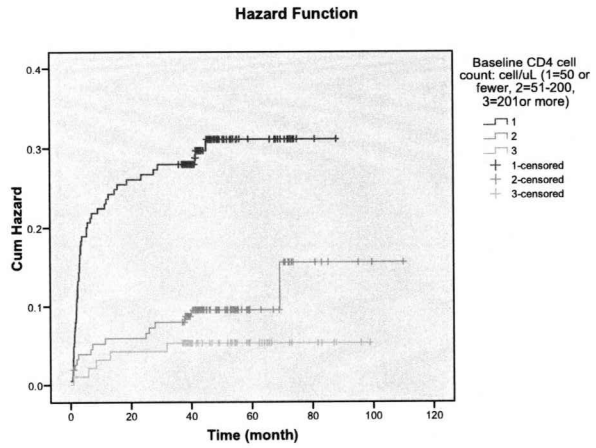


Being member of people who living with HIV/AIDS (PLHA) self-help group	 	0.20
Being naïve to ART	 	0.000*

Baseline CD4: cell/μL

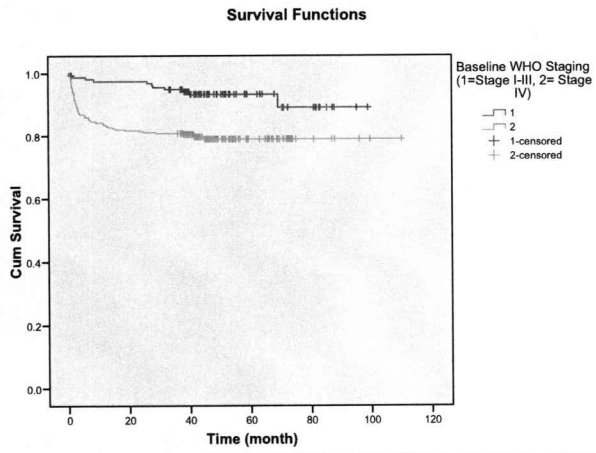
0.000*

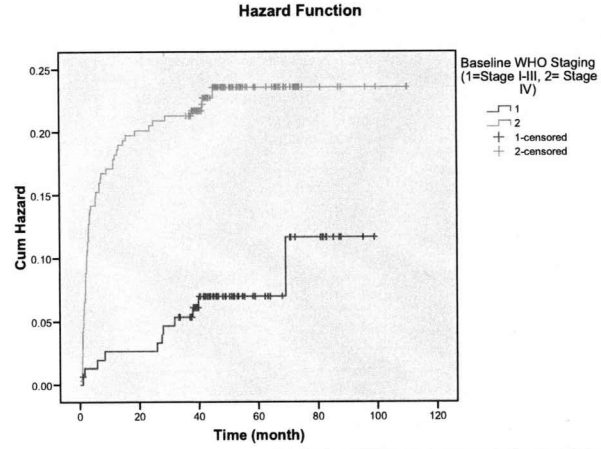




Baseline WHO staging

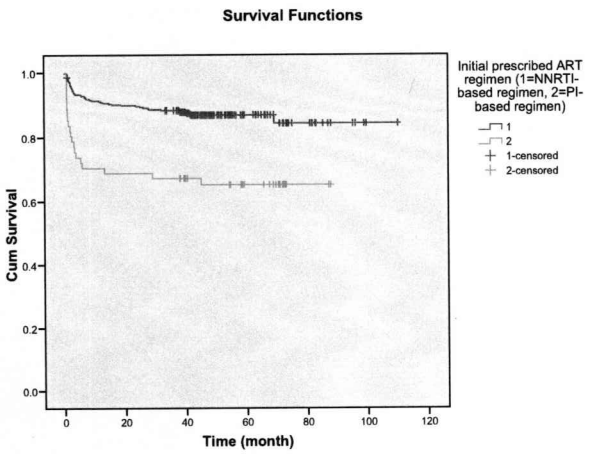
0.000*

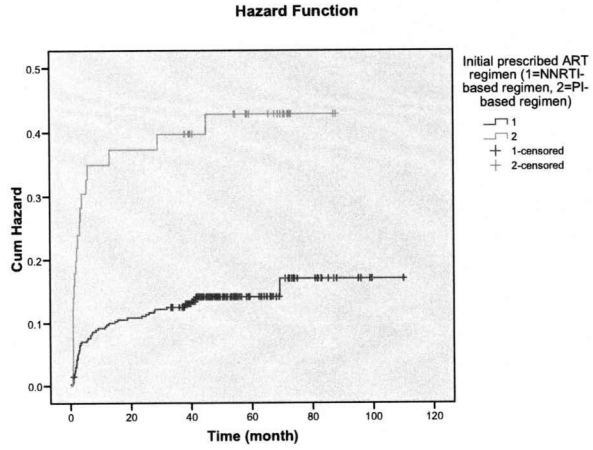




Initial prescribed regimen

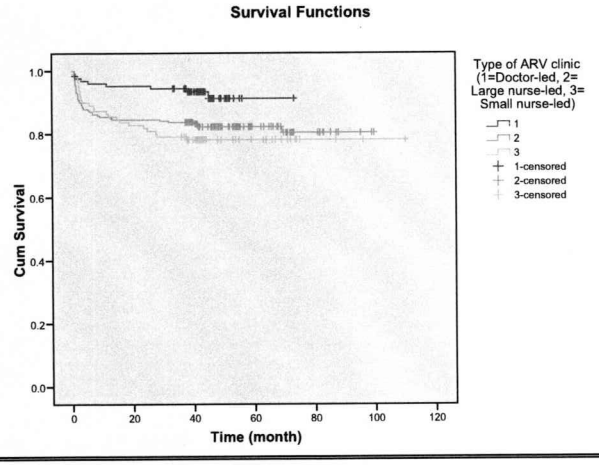
0.000*

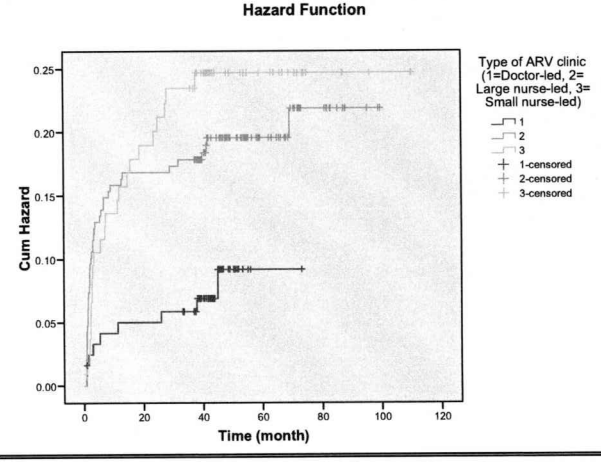




Type of ARV clinic

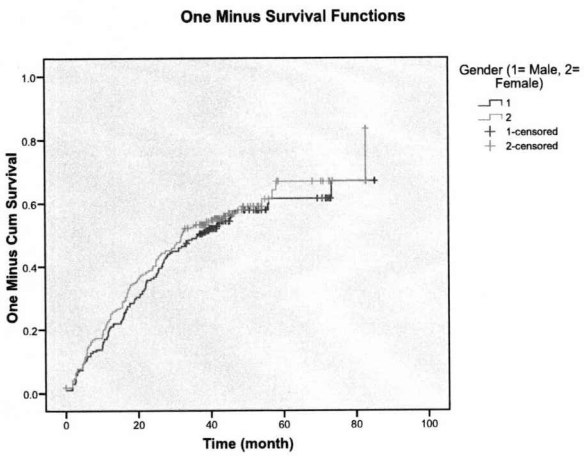
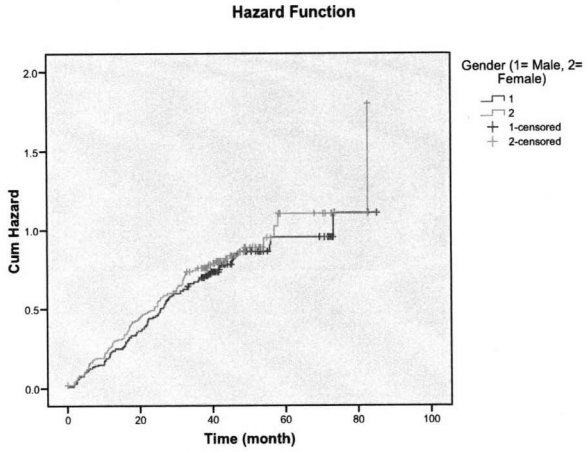
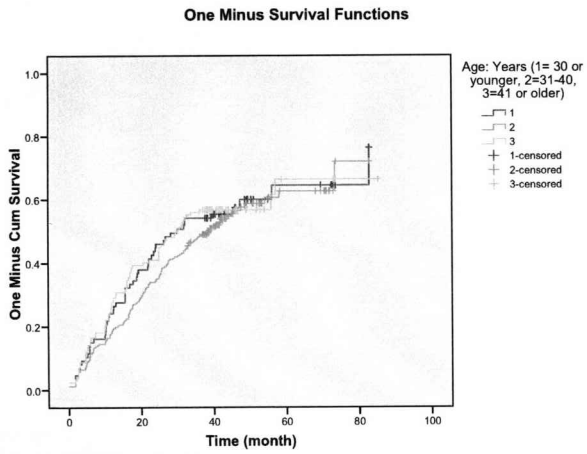
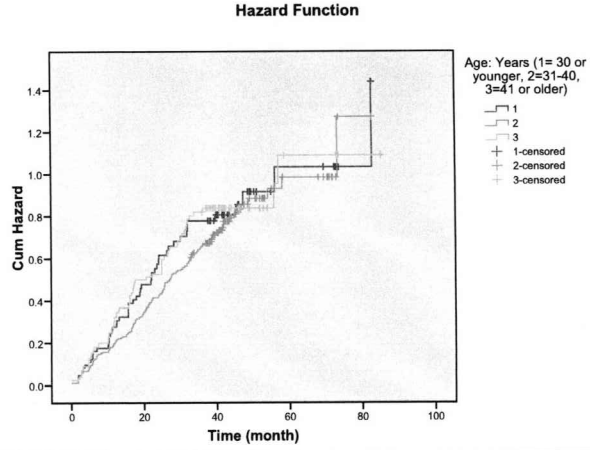
0.009*





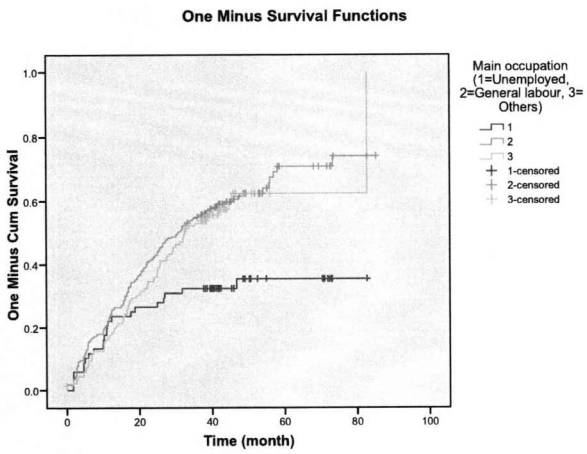
* Significant at P-value ≤ 0.05

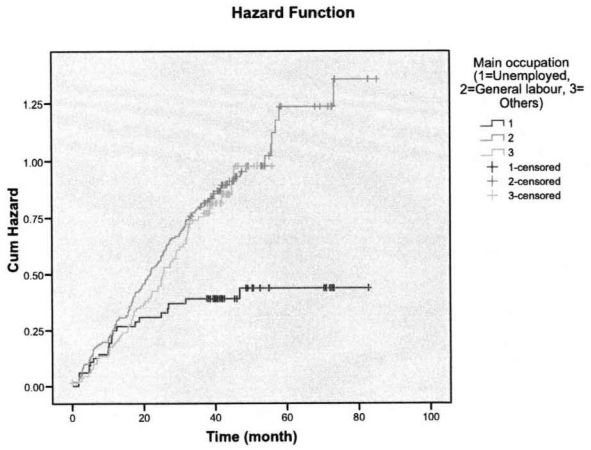
Table 6-2: Log rank test for potential predictors of having CD4 cell counts approach 200 cell/μL

Predictor	Time to event (1-survival)function	Hazard function	P-value
Gender			0.46
Age: Year			0.53

Main occupation

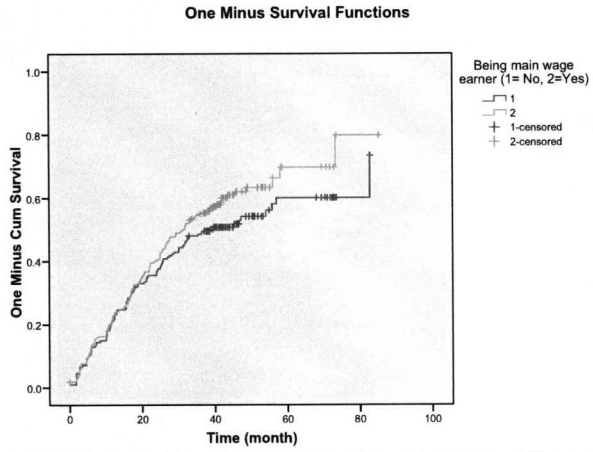
0.001*

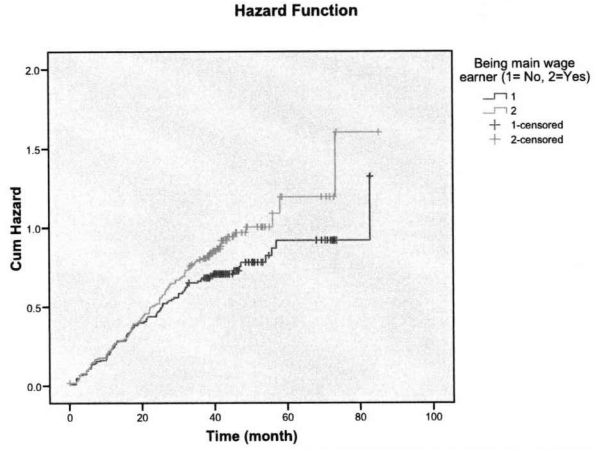


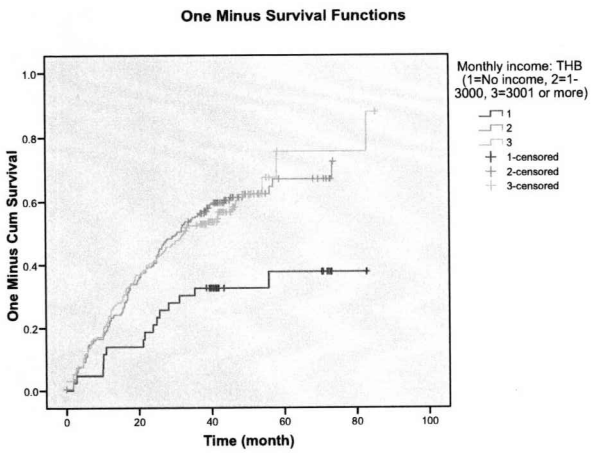
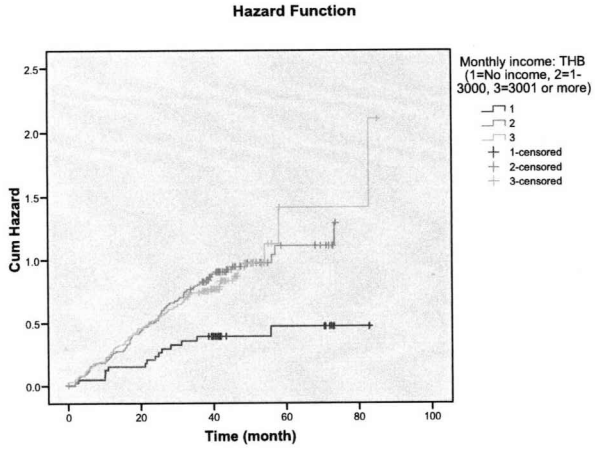
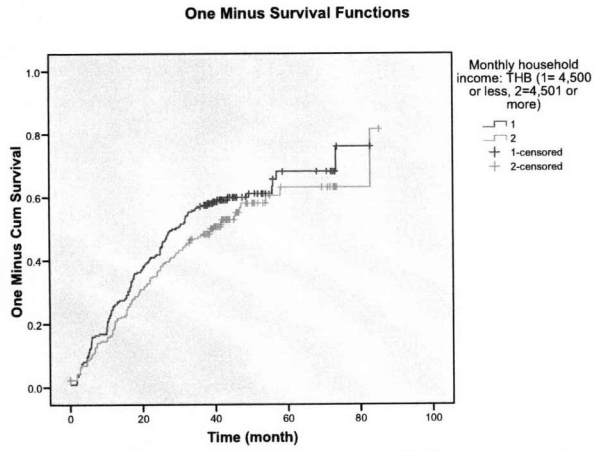
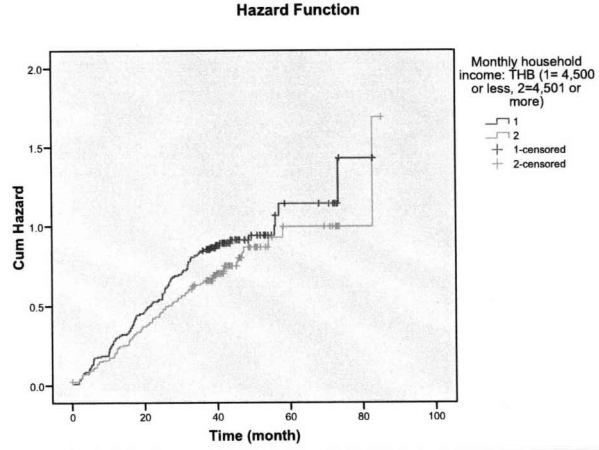


Being main wage earner

0.12

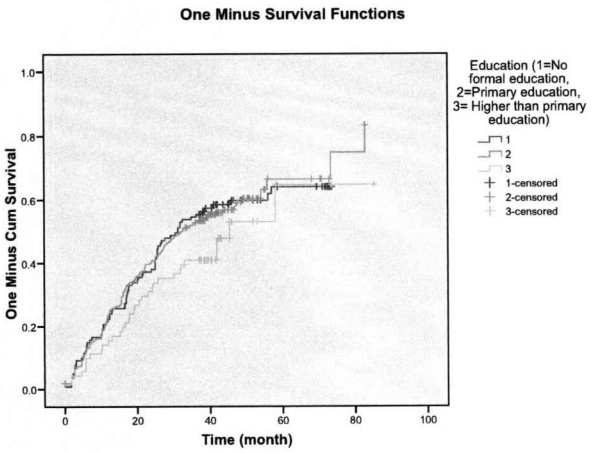


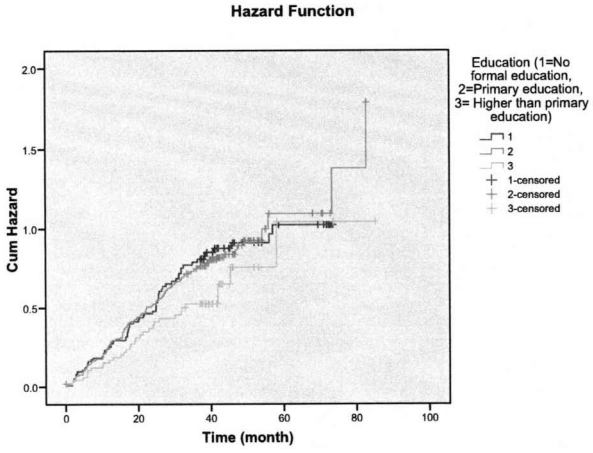


Monthly income: THB	 	0.005*
Monthly household income: THB	 	0.11

Education

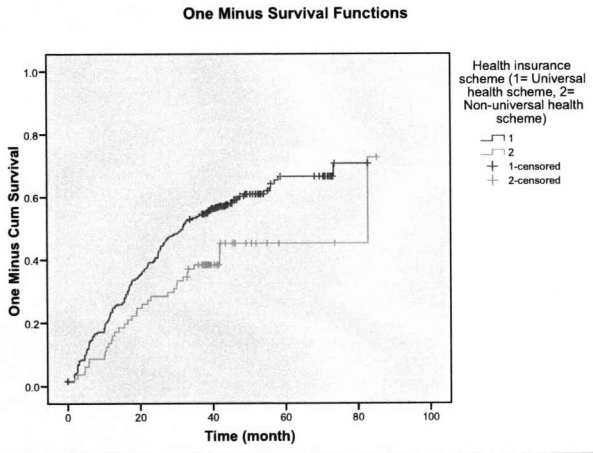
0.22

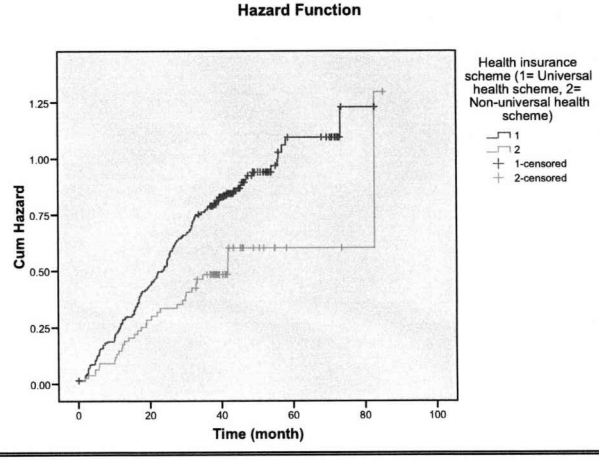


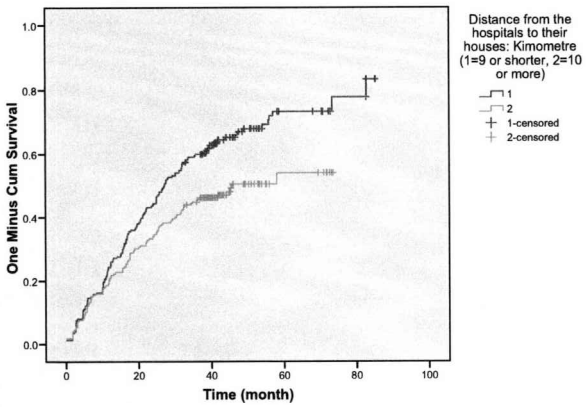
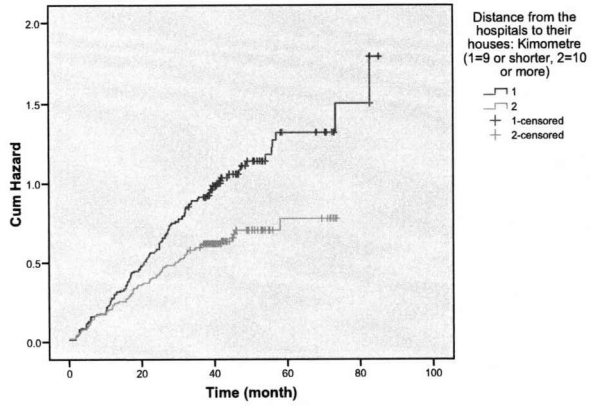
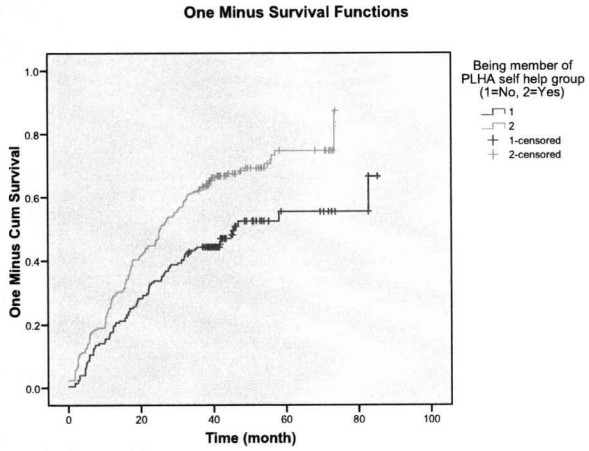
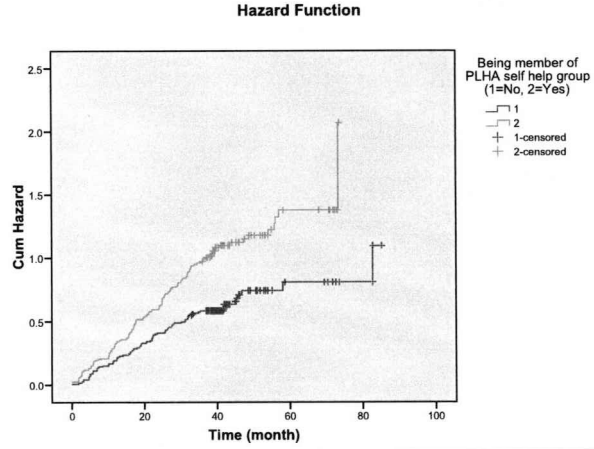


Health insurance scheme

0.009*

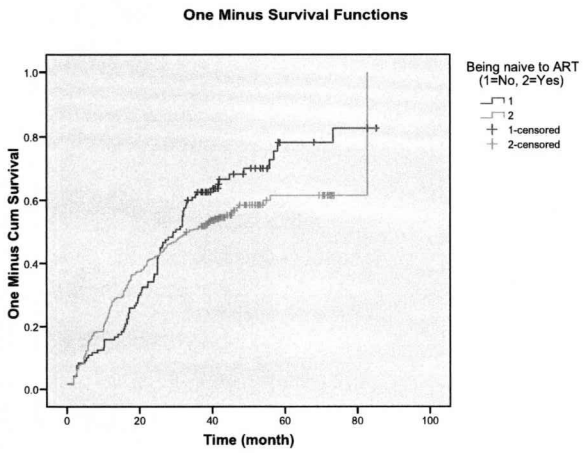


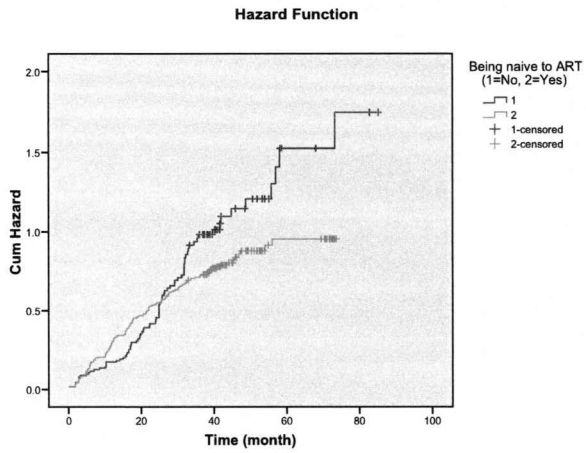


Distance between hospitals and their houses: Kilometre	 	0.001*
Being member of people who living with HIV/AIDS (PLHA) self-help group	 	0.000*

Being naïve to ART

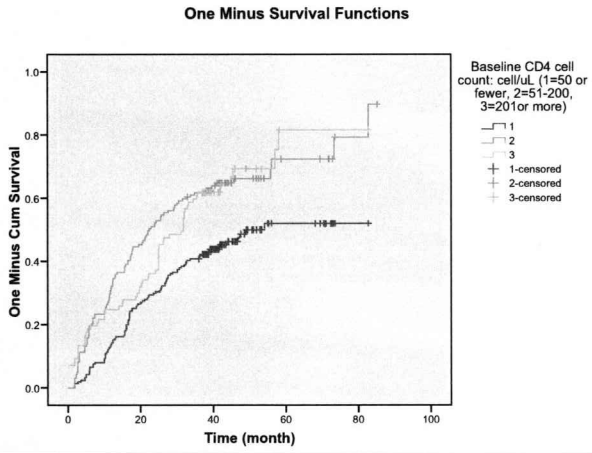
0.18

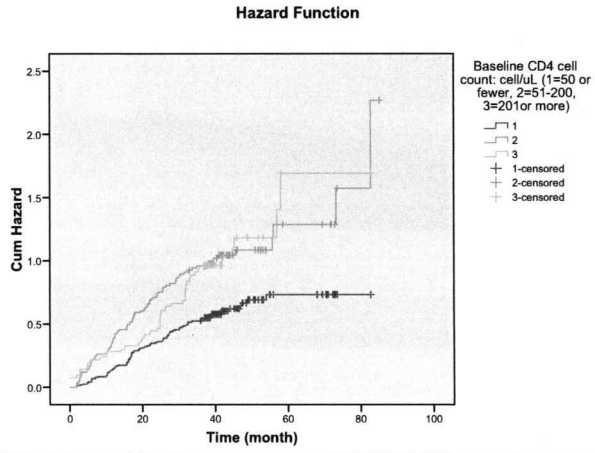




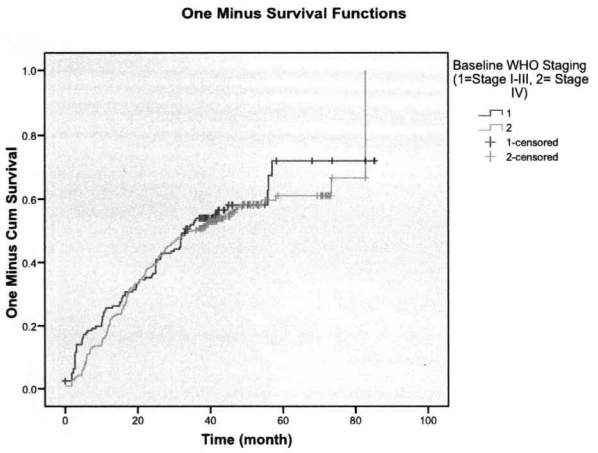
Baseline CD4: cell/μL

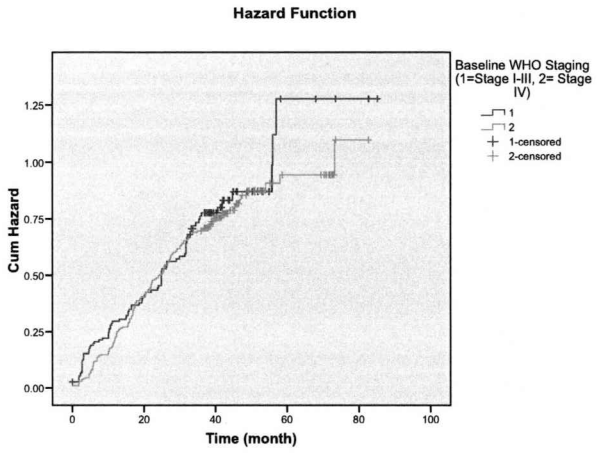
0.000*



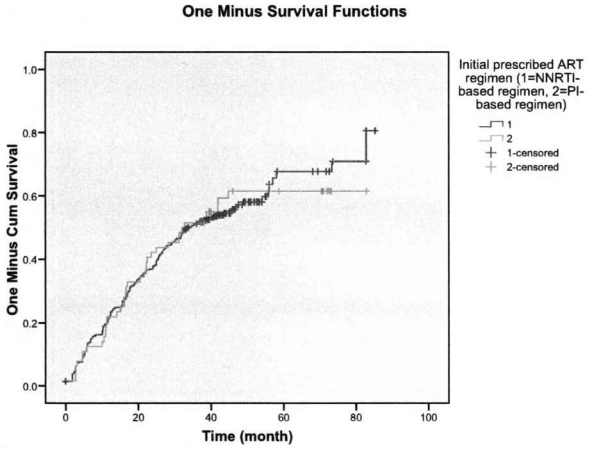


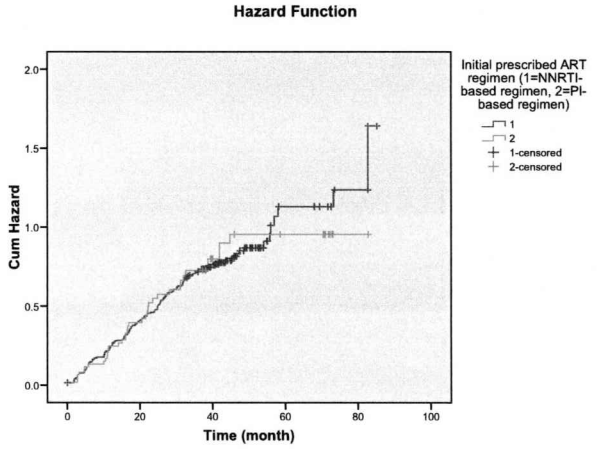
Baseline WHO staging 0.57



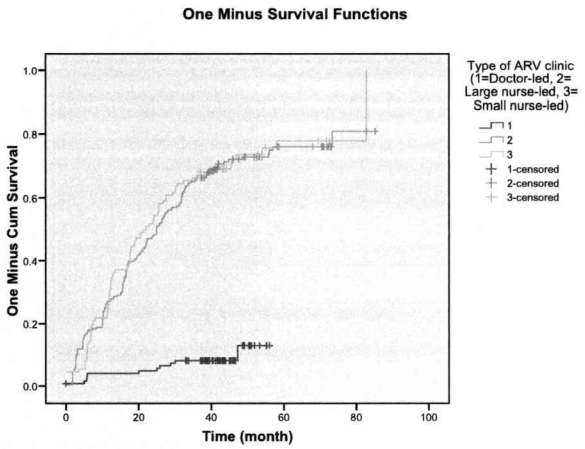


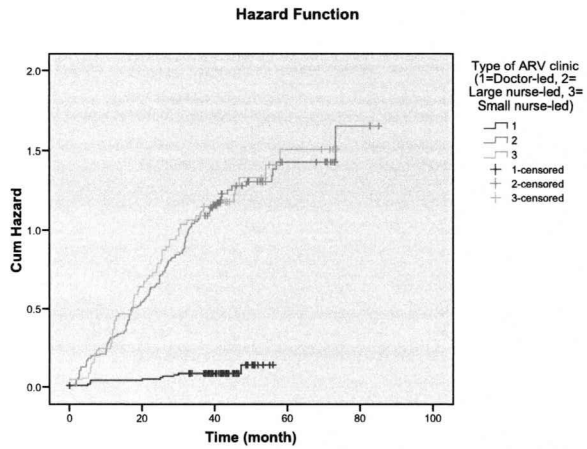
Initial prescribed regimen 0.91





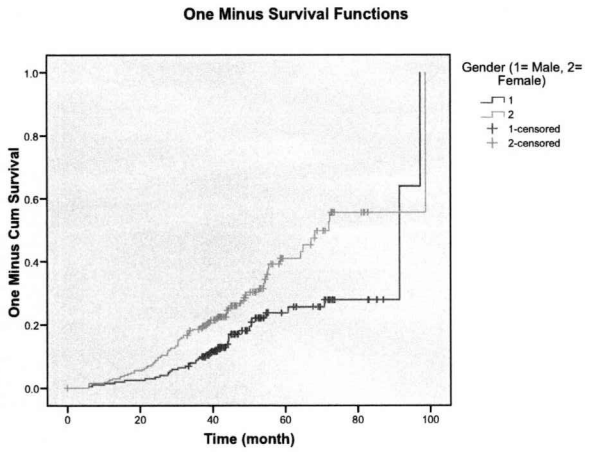
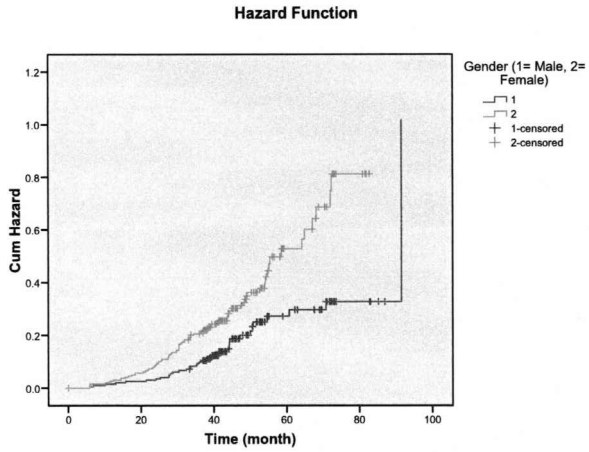
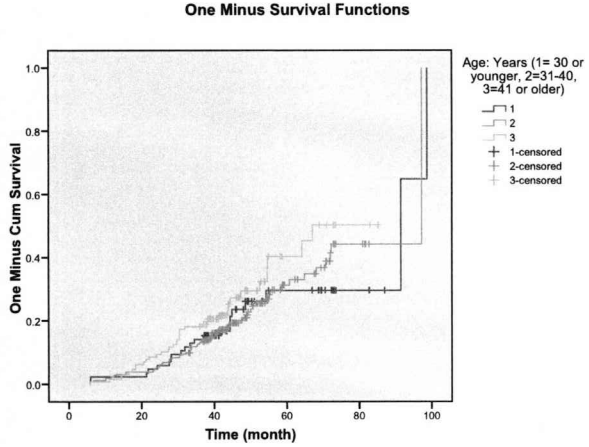
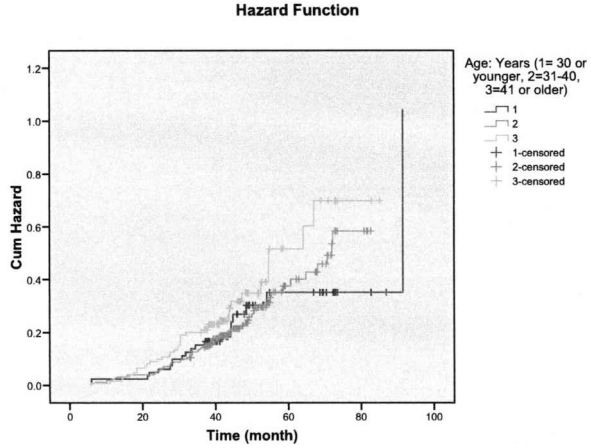
Type of ARV clinic	0.000*



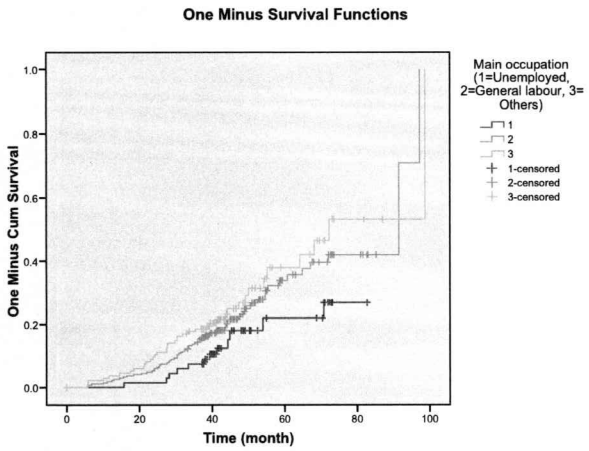


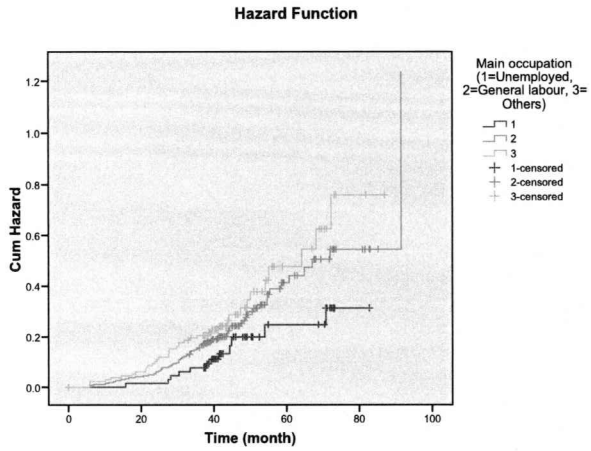
* Significant at P-value ≤ 0.05

Table 6-3: Log rank test for potential predictors of having CD4 cell counts approach 500 cell/μL

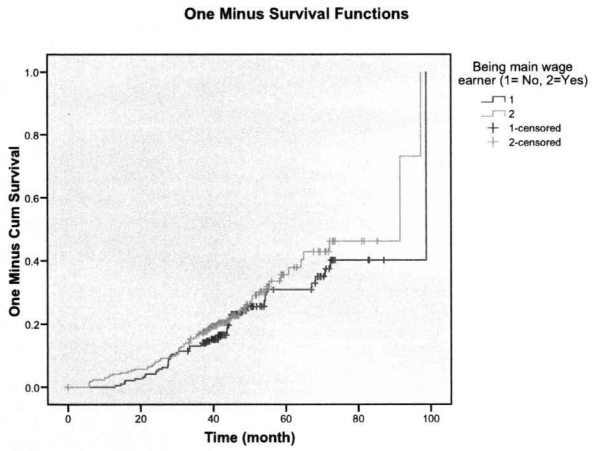
Predictor	Time to event (1-survival)function	Hazard function	P-value
Gender			0.001*
Age: Year			0.24

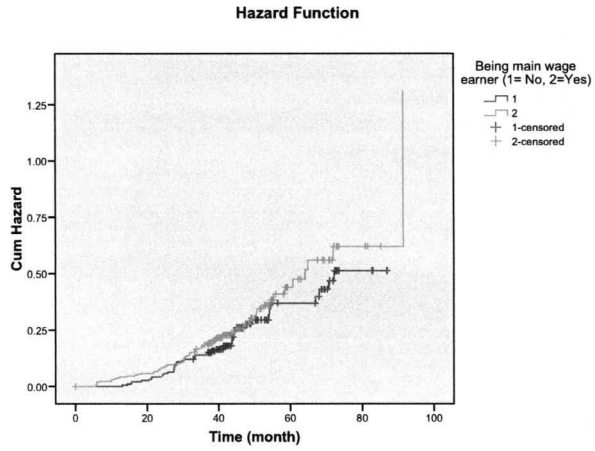
Main occupation 0.11

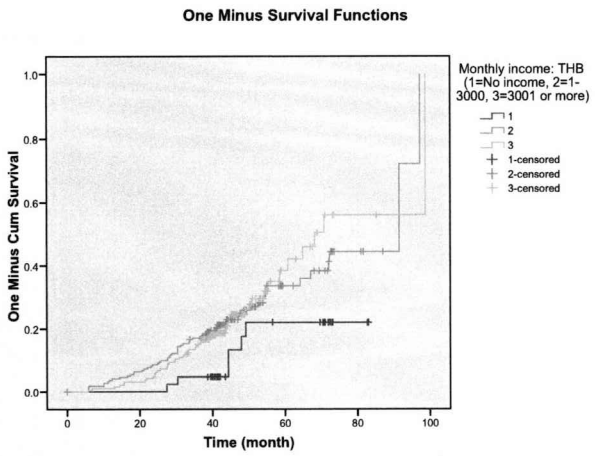
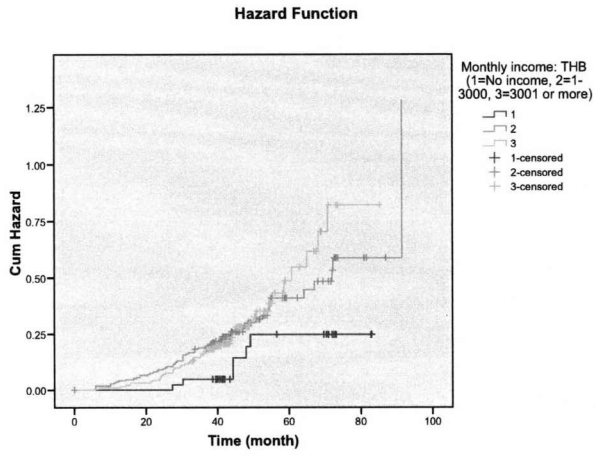
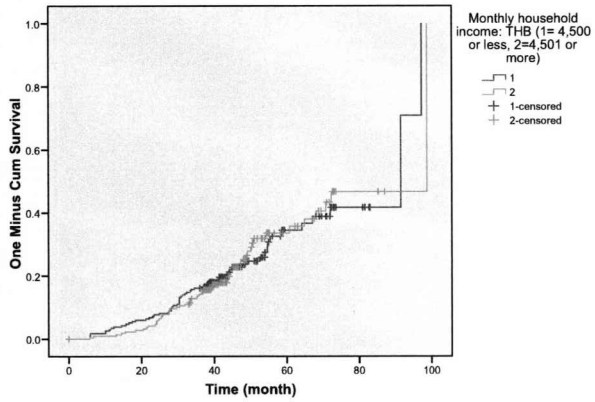
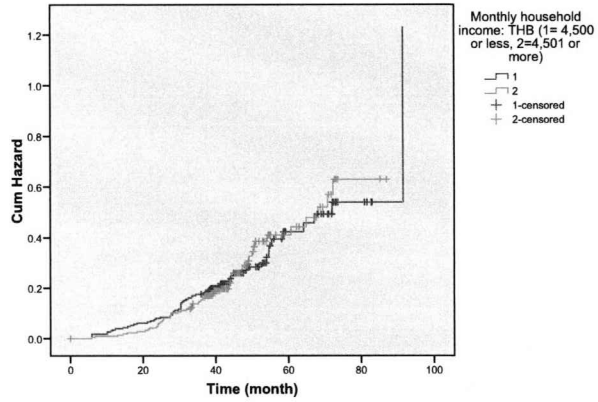




Being main wage earner 0.26

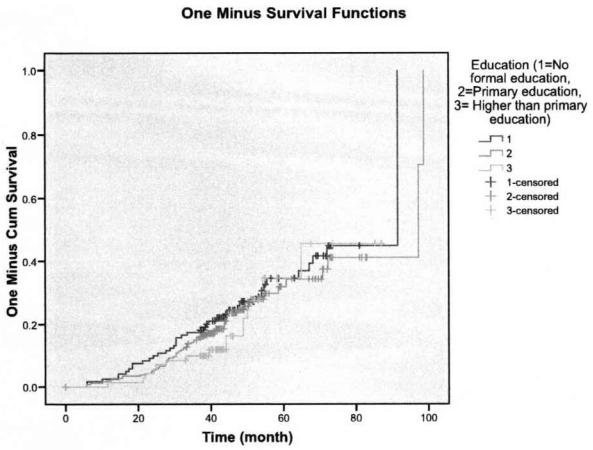


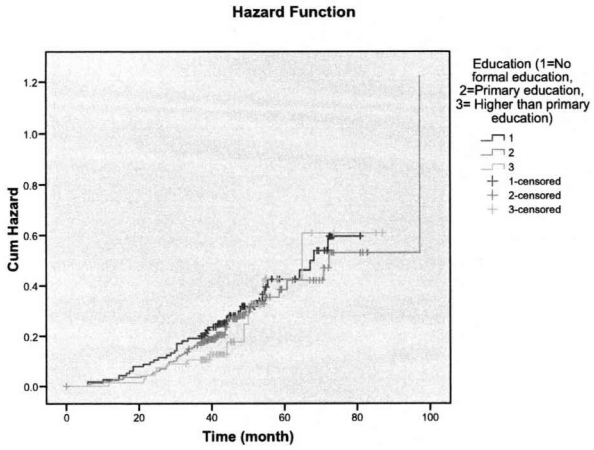


Monthly income: THB	 	0.048*
Monthly household income: THB	 	0.99

Education

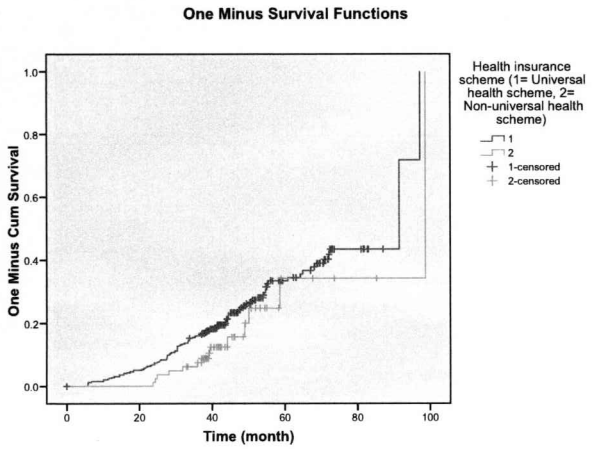
0.53

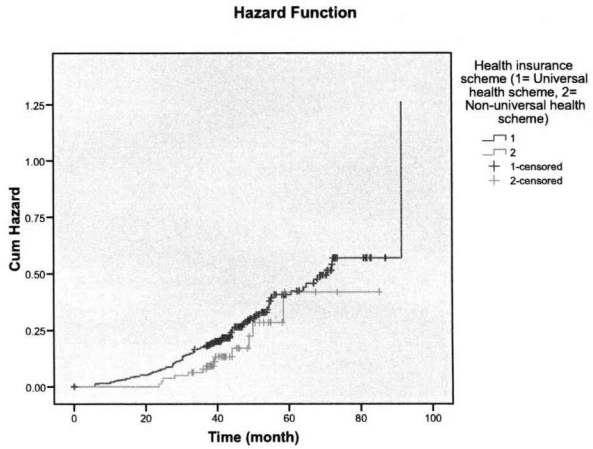


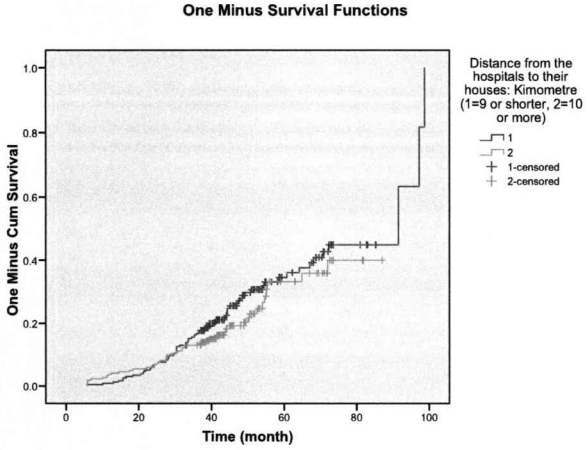
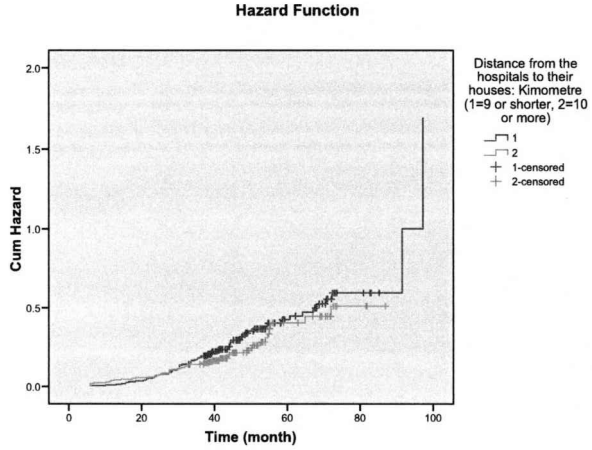
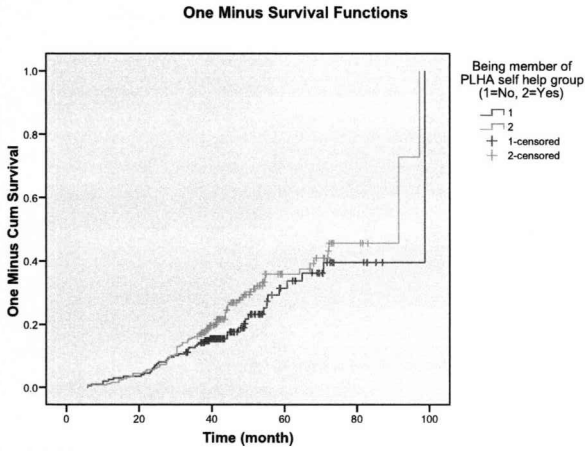
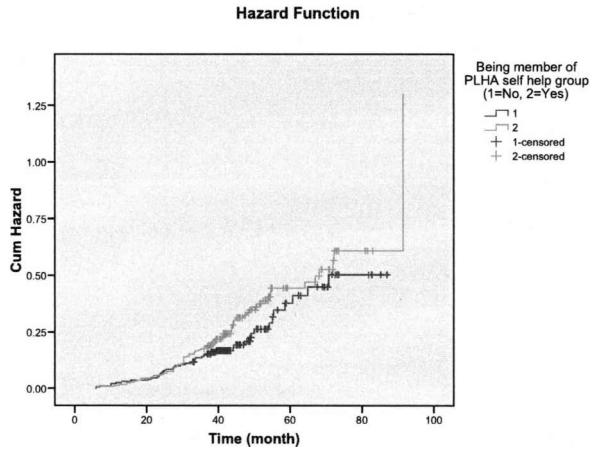


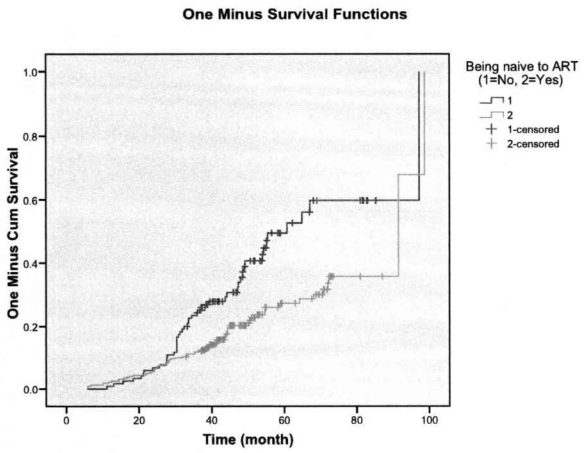
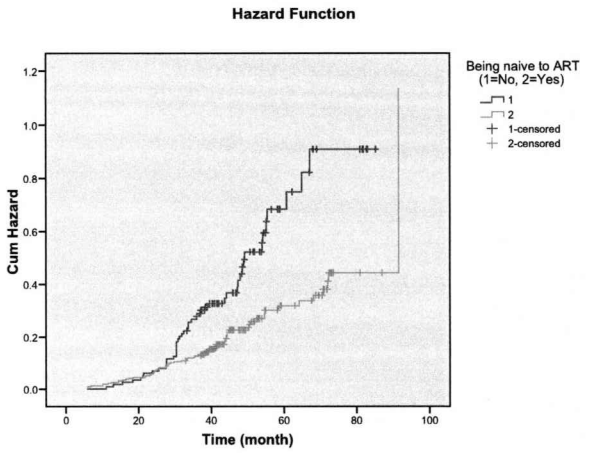
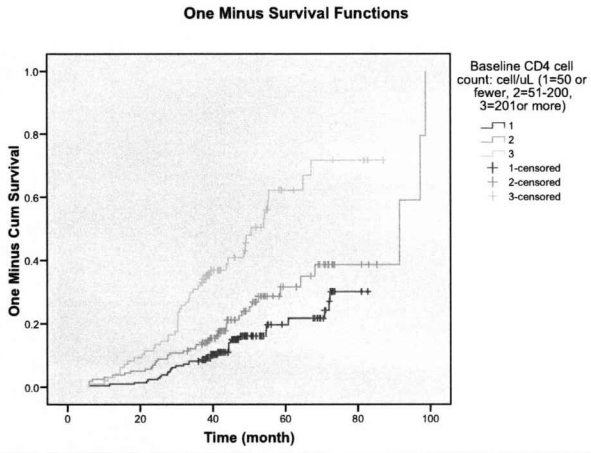
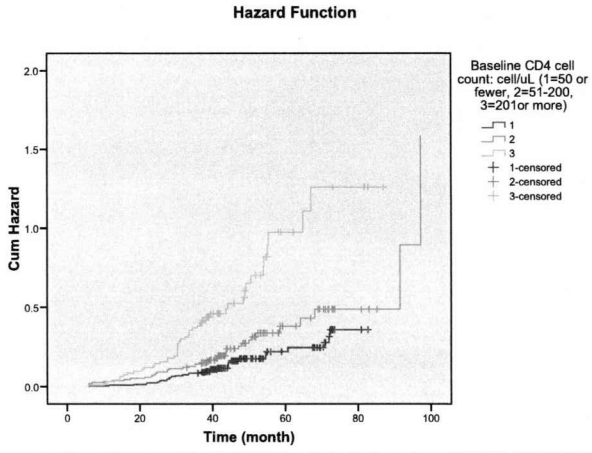
Health insurance scheme

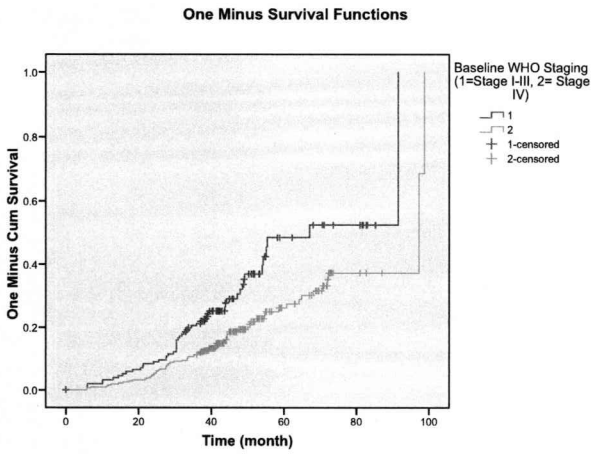
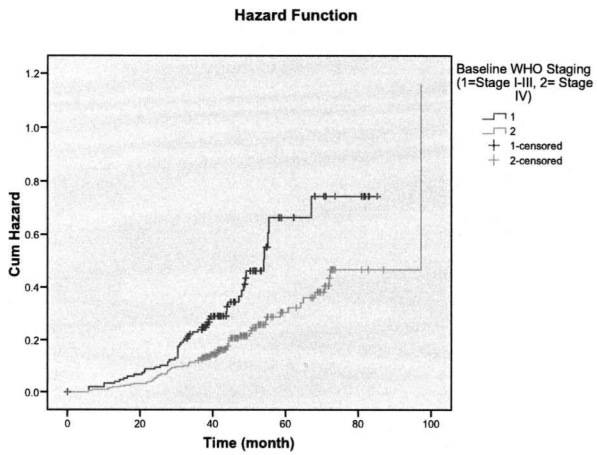
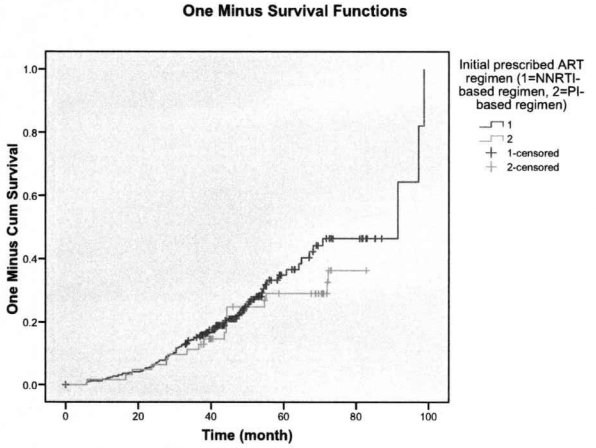
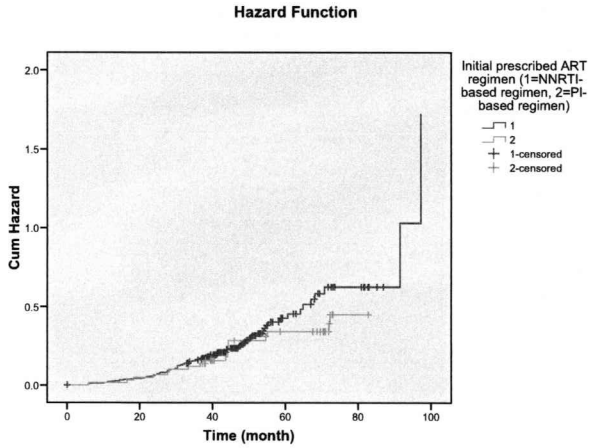
0.10



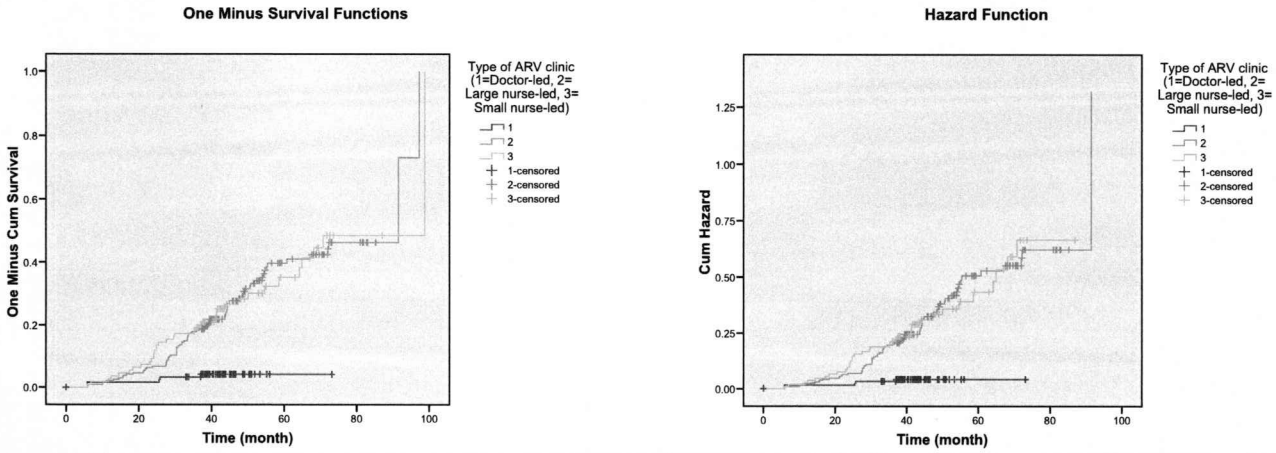


Distance between hospitals and their houses: Kilometre	 	0.22
Being member of people who living with HIV/AIDS (PLHA) self-help group	 	0.16

Being naïve to ART	 	0.000*
Baseline CD4: cell/μL	 	0.000*

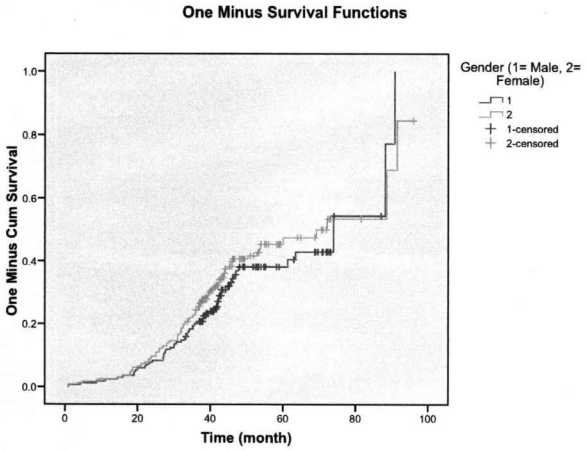
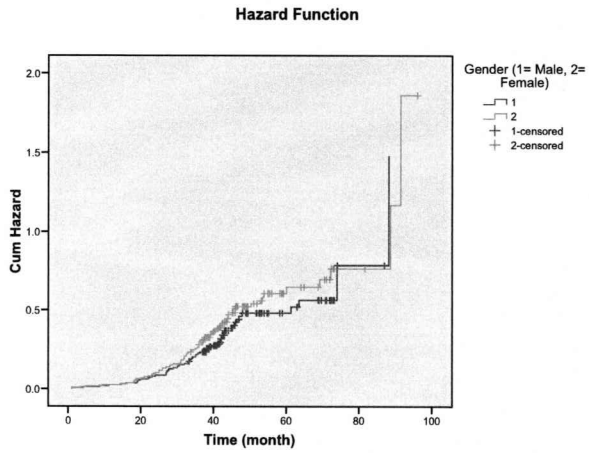
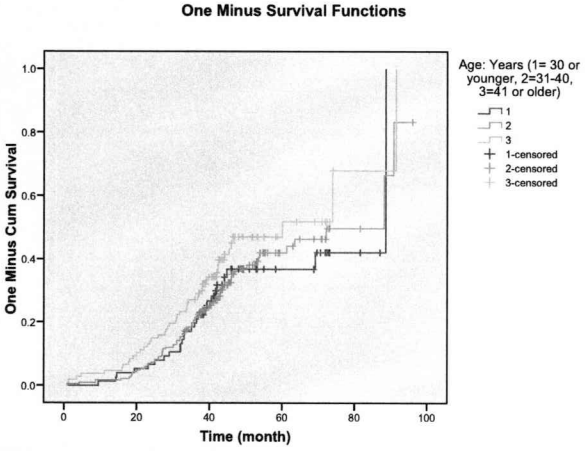
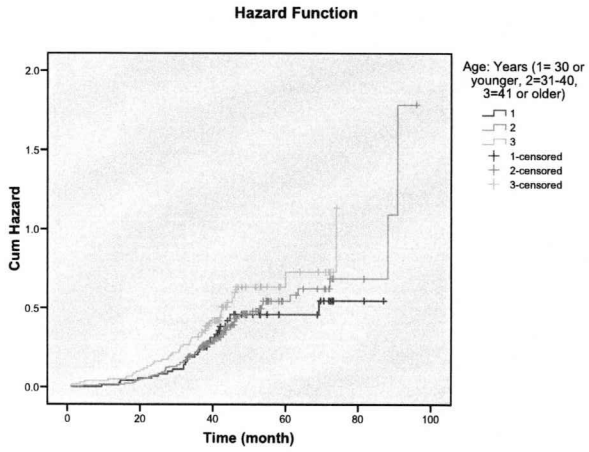
Baseline WHO staging	 	0.001*
Initial prescribed regimen	 	0.28

Type of ARV clinic	0.000*

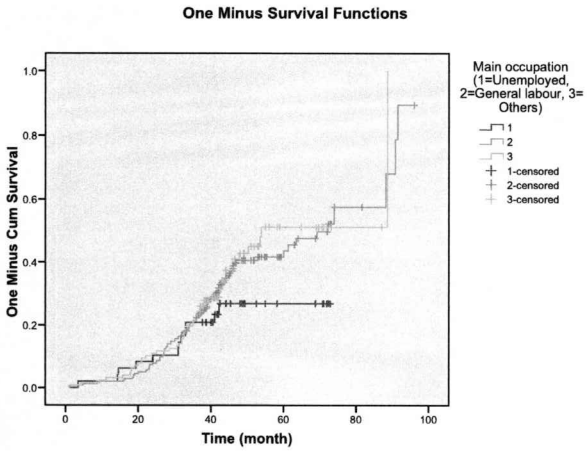


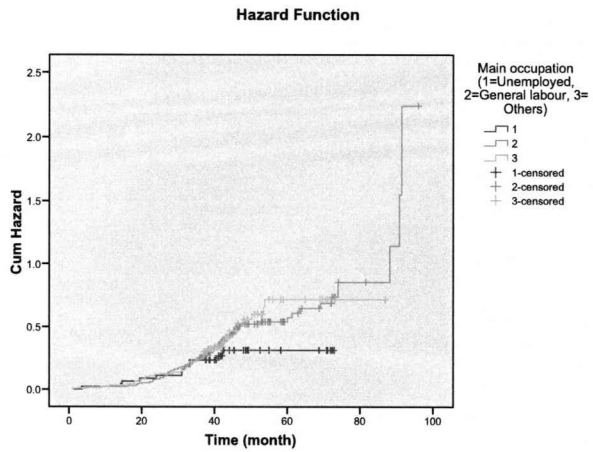
* Significant at P-value ≤ 0.05

Table 6-4: Log rank test for potential predictors of changing ART regimen

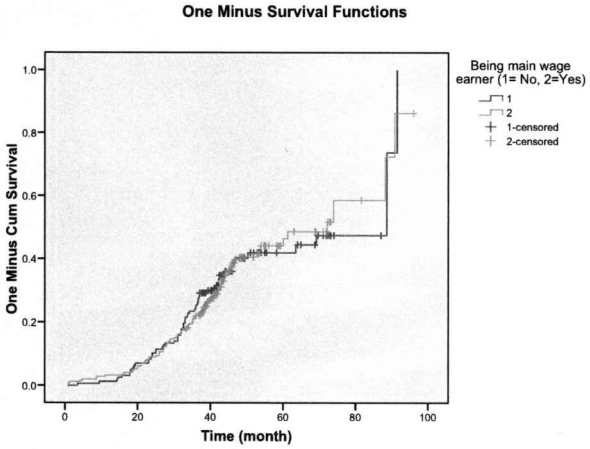
Predictor	Time to event (1-survival)function	Hazard function	P-value
Gender			0.30
Age: Year			0.23

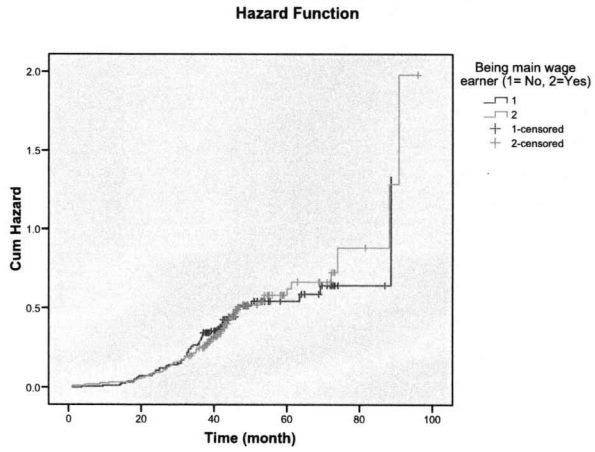
Main occupation 0.23





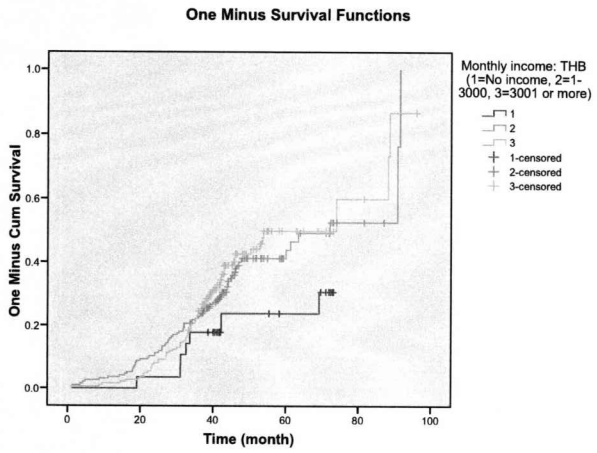
Being main wage earner 0.88

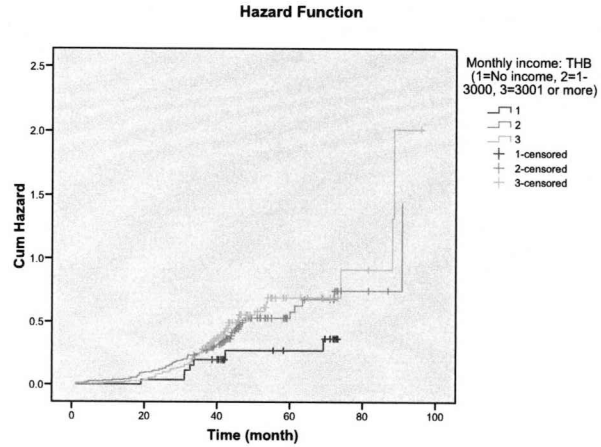




Monthly income: THB

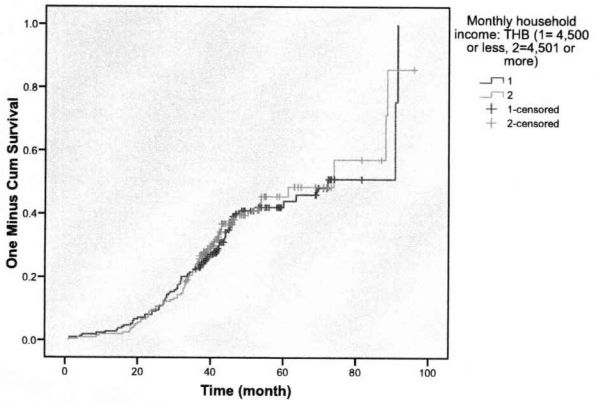
0.18

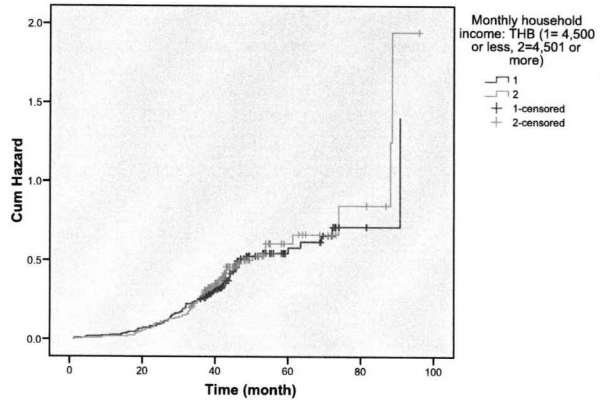




Monthly household income: THB

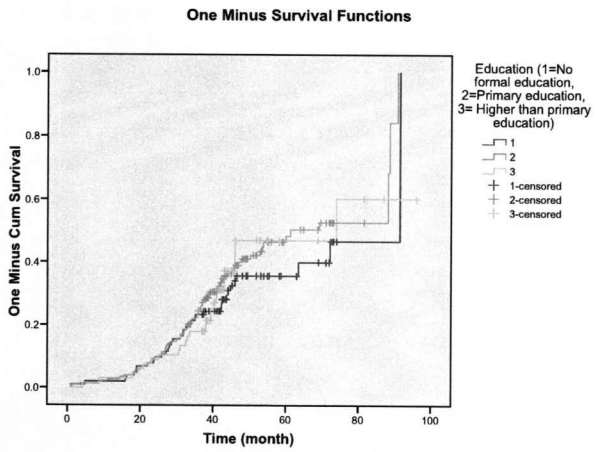
0.69

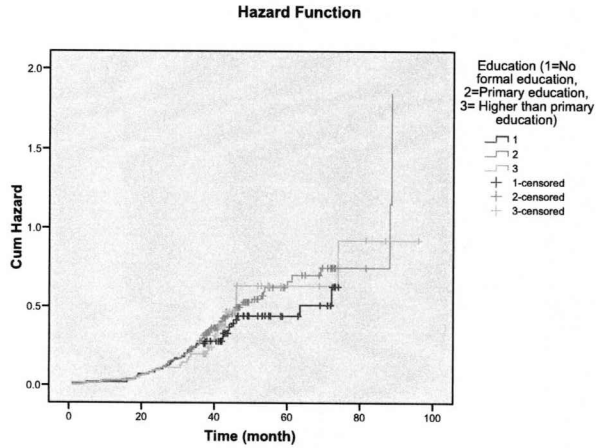




Education

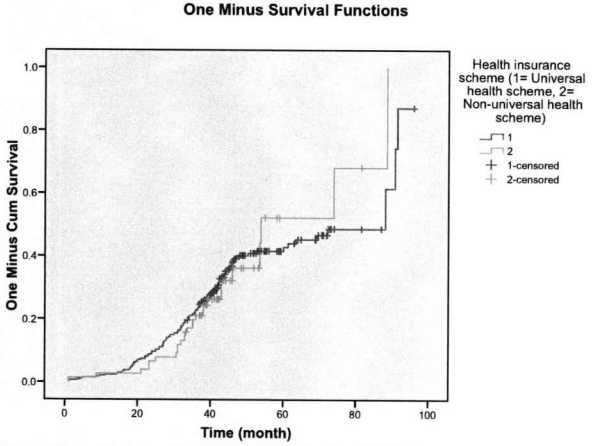
0.41

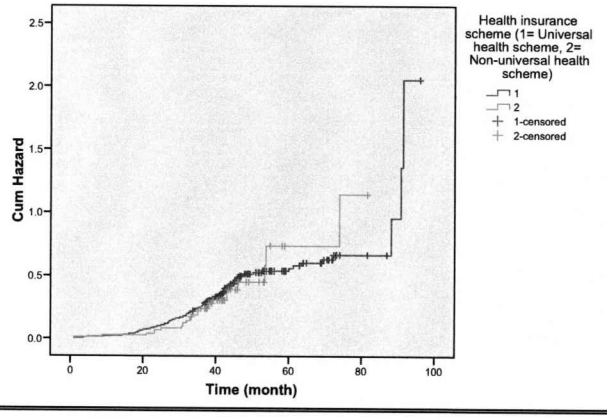


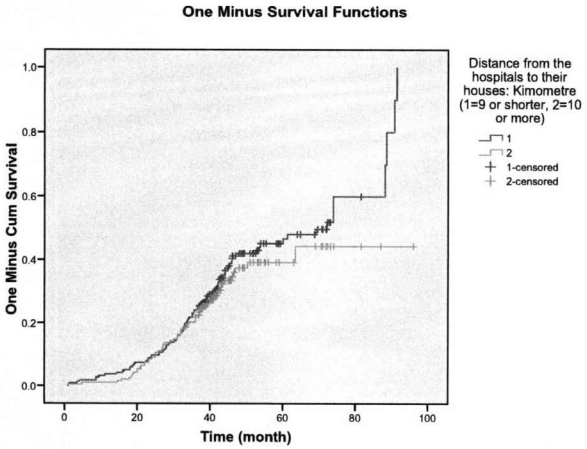
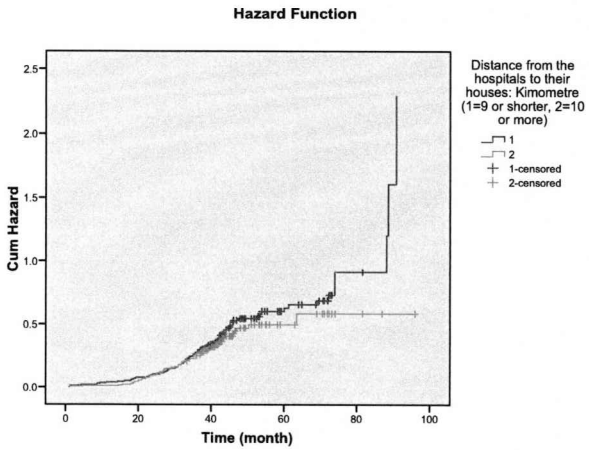
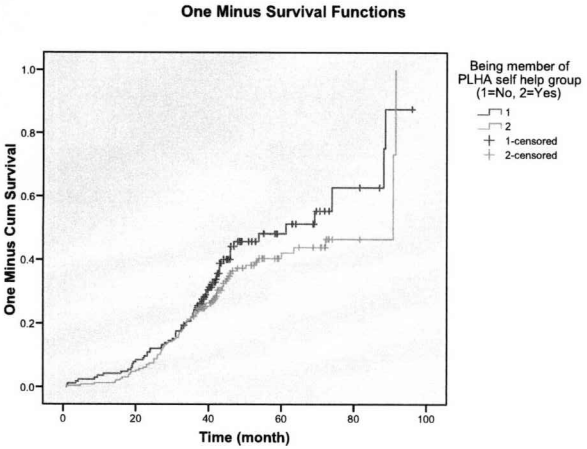
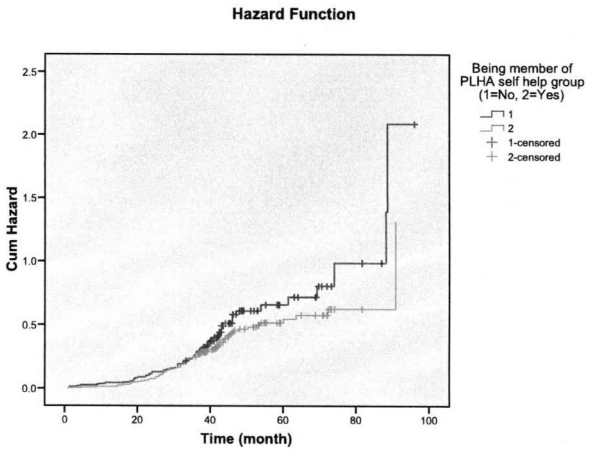


Health insurance scheme

0.94

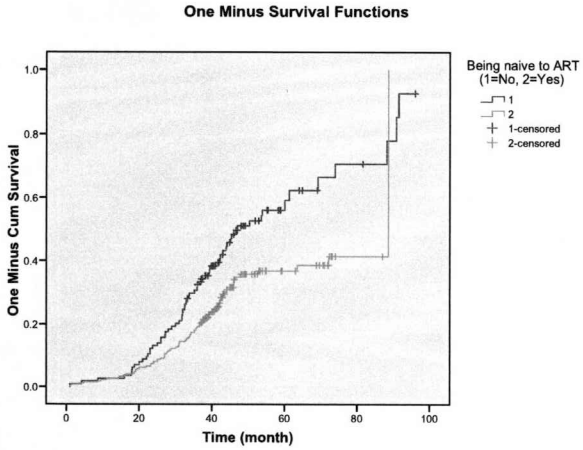


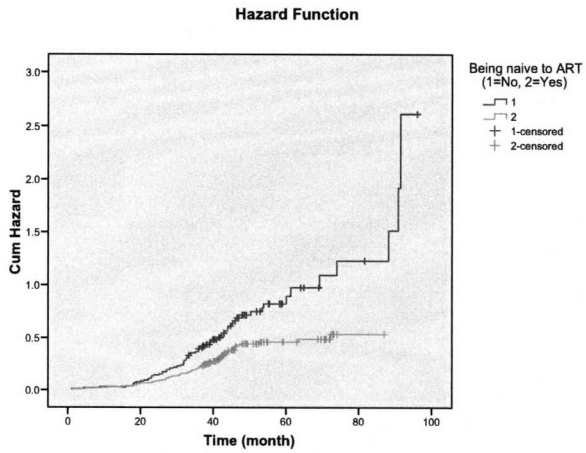


Distance between hospitals and their houses: Kilometre	 	0.30
Being member of people who living with HIV/AIDS (PLHA) self-help group	 	0.17

Being naïve to ART

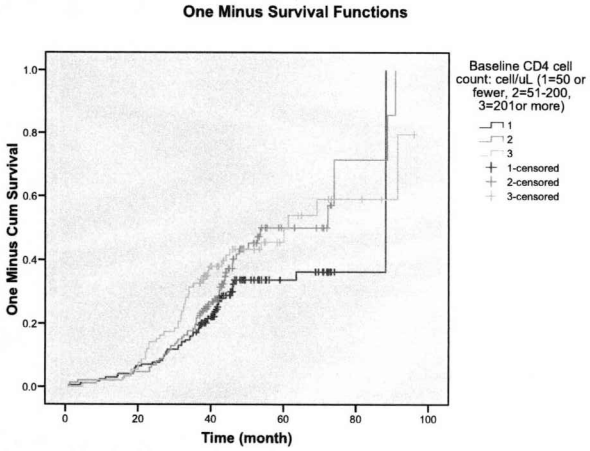
0.001*

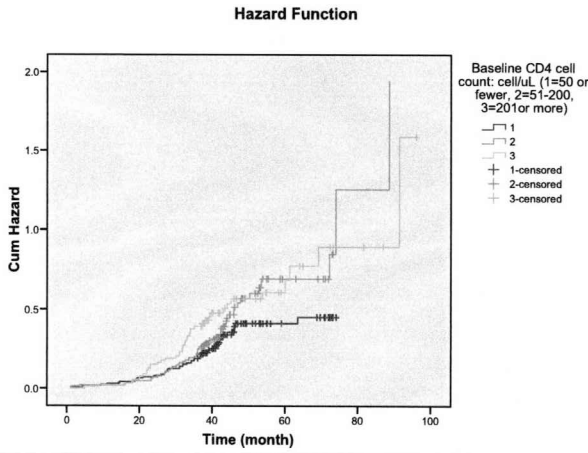




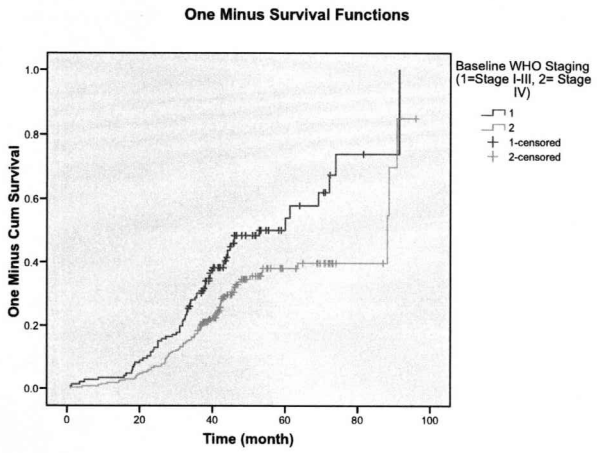
Baseline CD4: cell/µL

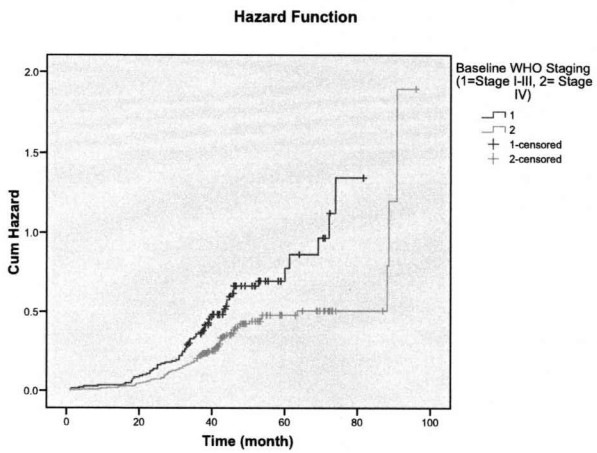
0.08



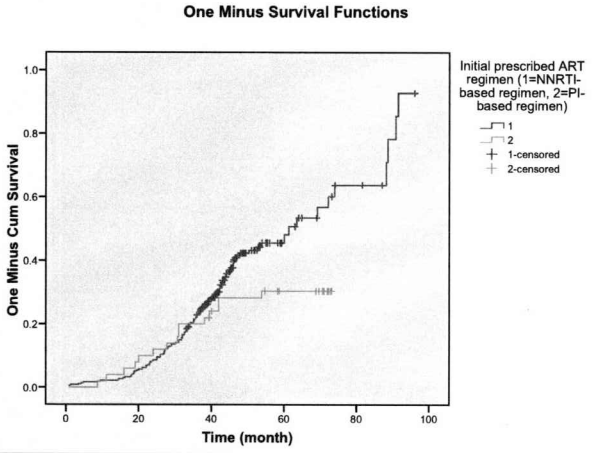


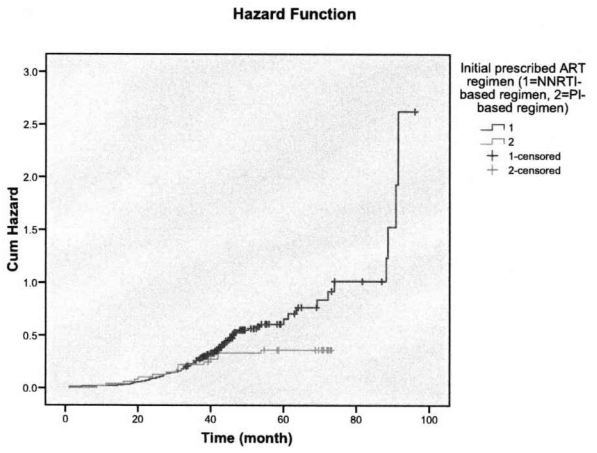
Baseline WHO staging 0.001*



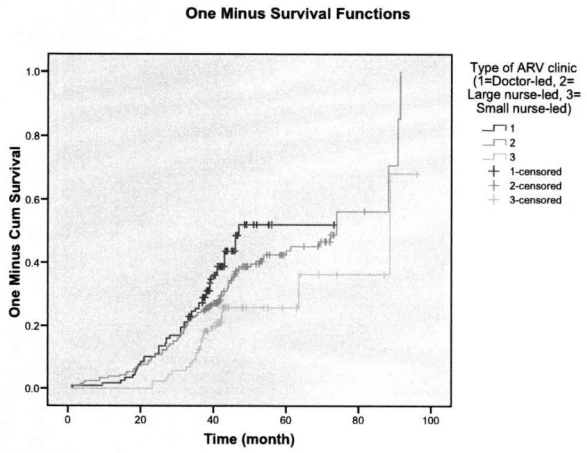


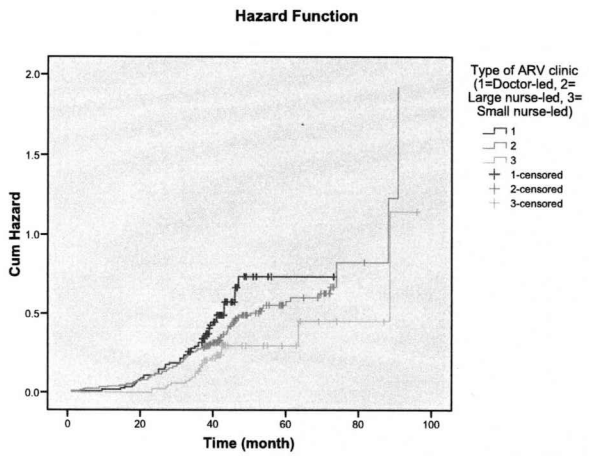
Initial prescribed regimen 0.028*





Type of ARV clinic	0.014*





* Significant at P-value ≤ 0.05

6.2 *Annex 2: The Cox proportional model for four treatment outcomes*

Table 6-5: Cox proportional hazard regression for mortality

Variable	Regression coefficient	Hazard ratio	P value
Male	0.64	1.90	0.04*
Age	0.01	1.01	0.52
Main occupation			
Unemployed	2.61	13.65	0.000*
General labourer	1.52	4.56	0.015*
Being main wage earner	0.02	1.02	0.96
Monthly income	-0.001	0.99	0.000*
Monthly household income	0.001	0.99	0.72
Education			
No formal education	-0.55	0.58	0.36
Primary education	-0.60	0.55	0.31
Universal heath scheme	0.25	1.28	0.67
Distance between the hospitals and their houses	0.01	1.01	0.45
Being member of PLHA self-help group	0.84	2.31	0.005*
Being naïve to the ART	-0.49	0.61	0.41
Baseline CD4 cell counts	-0.003	0.99	0.15
Baseline WHO stage IV	0.39	1.47	0.45
Initially prescribed with PI-based regimen	-0.60	0.55	0.14
Type of ARV clinic			
Doctor-led	-2.35	0.10	0.002*
Large nurse-led	-1.28	0.27	0.002*
Monthly household income*monthly income	0.000	1.00	0.000*

Table 6-6: Cox proportional hazard regression for having CD4 approached the level of 200cell/uL

Variable	Regression coefficient	Hazard ratio	P value
Male	-0.15	0.86	0.26
Age	-0.01	0.99	0.58
Main occupation			
Unemployed	-0.71	0.49	0.011*
General labourer	-0.38	0.68	0.018*
Being main wage earner	0.04	1.04	0.80
Monthly income	0.00	1.00	0.008*
Monthly household income	0.00	1.00	0.033*
Education			
No formal education	-0.13	0.88	0.59
Primary education	0.02	1.02	0.94
Universal heath scheme	0.25	1.29	0.26
Distance between the hospitals and their houses	-0.01	0.99	0.34
Being member of PLHA self-help group	0.35	1.42	0.018*
Being naïve to the ART	0.37	1.45	0.034*
Baseline CD4 cell counts	0.44	1.56	0.000*
Baseline WHO stage IV	-0.03	0.97	0.88
Initially prescribed with PI-based regimen	-0.03	0.97	0.89
Type of ARV clinic			
Doctor-led	-2.68	0.07	0.000*
Large nurse-led	-0.10	0.90	0.57

Table 6-7: Cox proportional hazard regression for having CD 4 count approached the level of 500 cell/uL

Variable	Regression coefficient	Hazard ratio	P value
Male	-0.63	0.53	0.004*
Age	-0.00	1.00	0.90
Main occupation			
Unemployed	-0.22	0.80	0.58
General labourer	-0.50	0.61	0.04
Being main wage earner	0.17	1.20	0.47
Monthly income	0.00	1.00	0.08
Monthly household income	0.00	1.00	0.39
Education			
No formal education	0.22	1.25	0.58
Primary education	0.17	1.19	0.63
Universal heath scheme	0.76	2.14	0.05
Distance between the hospitals and their houses	0.00	1.00	0.30
Being member of PLHA self-help group	0.09	1.09	0.69
Being naïve to the ART	-0.15	0.86	0.55
Baseline CD4 cell counts	0.60	1.82	0.000*
Baseline WHO stage IV	-0.23	0.80	0.44
Initially prescribed with PI-based regimen	0.17	1.18	0.61
Type of ARV clinic			
Doctor-led	-2.66	0.07	0.000*
Large nurse-led	-0.29	0.75	0.33

Table 6-8: Cox proportional hazard regression for duration on the first-line regimen

Variable	Regression coefficient	Hazard ratio	P value
Male	-0.01	0.99	0.97
Age	0.03	1.03	0.05
Main occupation			
Unemployed	-0.42	0.66	0.26
General labourer	-0.26	0.77	0.23
Being main wage earner	-0.05	0.95	0.80
Monthly income	0.00	1.00	0.45
Monthly household income	0.00	1.00	0.41
Education			
No formal education	0.00	1.00	0.99
Primary education	0.30	1.35	0.27
Universal heath scheme	0.08	1.09	0.75
Distance between the hospitals and their houses	-0.01	0.99	0.29
Being member of PLHA self-help group	-0.16	0.85	0.43
Being naïve to the ART	-0.24	0.79	0.25
Baseline CD4 cell counts	-0.02	0.98	0.90
Baseline WHO stage IV	-0.33	0.72	0.19
Initially prescribed with PI-based regimen	-0.44	0.64	0.17
Type of ARV clinic			
Doctor-led	0.82	2.28	0.006*
Large nurse-led	0.46	1.58	0.11

6.3 Annex 3: Terminology and definition

Terminology used in this study is mostly presented in form of "MeSH (Medical Subject Heading" which is the U.S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/PubMed. MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts. Please visit http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh for more information about MeSH

1. Antiretroviral Therapy, Highly Active (HAART, Highly Active Antiretroviral Therapy): Drug regimens, for patients with HIV infections that aggressively suppress HIV replication. The regimens usually involve administration of three or more different drugs including a protease inhibitor. Other synonyms include HAART, Highly Active Antiretroviral Therapy, antiretroviral treatment)

2. Developing country: Countries in the process of change directed toward economic growth, that is, an increase in production, per capita consumption, and income. The process of economic growth involves better utilization of natural and human resources, which results in a change in the social, political, and economic structure

3. Developed country: Countries that have reached a level of economic achievement through an increase of production, per capita income and consumption, and utilization of natural and human resources. Another related term is "High income country" is defined by the World Bank as a country with a Gross National Income per capita of $11,116 or more[1]. While the term "high income" may be used interchangeably with "First World" and "developed country," the technical definitions of these terms differ. The term "first world" commonly refers to those prosperous countries that aligned

[1] http://go.worldbank.org/D7SN0B8YU0

themselves with the U.S. and NATO during the cold war. Several institutions, such as the Central Intelligence Agency (CIA) or International Monetary Fund (IMF), take factors other than high per capita income into account when classifying countries as "developed" or "advanced economies." According to the United Nations, for example, some high income countries may also be developing countries. The GCC (Persian Gulf States) countries, for example, are classified as developing high income countries. Thus, a high income country may be classified as either developed or developing[2]

4. Doctor-led clinic: clinic that cares of are principally delivered by physicians including general practitioners, family doctors, specialist doctor or general internists (Miles, Penny et al. 2003); (Fitzsimmons, Hawker et al. 2005); (Griffiths, Edwards et al. 2007)

5. Nurse-led clinic: clinic that any qualified nurse working as a substitute to doctor. This could include nurse practitioners, clinical nurse specialists, advanced practice nurses and practice nurses. The nurse must have been the identified leader of the clinical team for a majority of patients in the unit. Where leadership is unclear, nurses having the authority to admit and discharge patients operationally defined nurse-management of care with intention of reducing cost or addressing workforce shortages. However, the nurse-led clinic is by some means usually operated under supervision or collaboration with physician (Caine, Sharples et al. 2002); (Miles, Penny et al. 2003); (Fitzsimmons, Hawker et al. 2005); (Griffiths, Edwards et al. 2007).

[2] http://www.unctad.org/en/docs/tdstat30_enfr.pdf

6.4 Annex 4: Questionnaire

6.4.1 Consent Form for Research Participants

A. PURPOSE AND BACKGROUND

In Thailand, it was estimated that 80% of HIV/AIDS people are receiving antiretroviral therapy (ART) through the national government antiretroviral therapy program since the start of the programme in 2001. However, evidences of the impact of ART on survival and other outcomes such as survival and health-related quality of life as well as others factors influence the treatment outcomes in Thailand are still scarce. To identify the impacts of ART programme, Dr. Thammasorn Piriyasupong, and his colleagues from Khon Kaen Hospital, Ministry of Public Health are now evaluating the outcomes of the antiretroviral therapy (ART) programme under Ministry of Public Health and exploring factors contributing to its success. This information from this interview will be used to see whether health-related quality of life has changed over time

B. SELECTION

I am being asked to participate in this study because I am currently on ART in the programme and previously contributed to the researcher's study

C. PROCEDURES

If I agree to be in this study, the following will occur:

I will talk with a trained interviewer who will go through a series of questions in relation to health-related quality of life with me. The interview will last approximately 20 minutes and can be done now. The interview contains questions about my living situation, working and living function, health status and other related issues. Interviews will be conducted in place where convenient for me. Interviews will be conducted at a

pre-arrange time that convenient and causes minimum disruption toward routine, agreed by the hospitals directors.

The given information will be coded (no names will be used). The code will be kept in a locked file and only Dr. Thammasorn and his co-investigators will have access to it. The code and all identifiers such as names, addresses, and phone numbers will be destroyed at the end of the study. Therefore, no one will be able to link back to me. All data are considered as strictly confidential.

D. RISK/DISCOMFORTS

Some of the topics in the interview are very personal and I may feel uncomfortable talking about them. However, I am free to decline to answer any questions I do not wish to answer or to stop the interview at any time. Also, if I feel the need to talk to someone for further counselling and support at the end of the interview, I will be given a referral by my interviewer.

E. CONFIDENTIALITY

Participation in research may involve a loss of privacy; however, my records will be handled as confidentially as possible. The researchers are doing the study in such a way that I will be anonymous. Only researchers directly involved in the study will have access to my interview. I will not give the researchers my name and no identifying information unique to me will be asked so my answers cannot be linked to me when the interview is over. Study information will be coded and kept in locked files at all times. No names will be used in any reports or publications that may result from this study.

F. BENEFITS

I may not benefit directly from this interview, however all of the information I give may lead to a better understanding of the services available to people with the HIV/AIDS and how to improve those services in relation to antiretroviral therapy.

G. ALTERNATIVES

I am completely free to choose not to participate in this study.

H. COSTS

There will be no costs to me as a result of taking part in this study.

I. CONTACT

I have talked to Dr. Thammasorn or one of his research associates about this study and have had my questions answered. If I have further questions about the study, or should I have any comments or concerns about participation in this study, I may contact the investigator at

Dr. Thammasorn Piriyasupong

Khon Kaen Hospital,

Khon Kaen Thailand 40000

Call: (+66) 85 0006261, (+66) 85 854 6523

Fax: (+66) 43 236 789 ext 1603

E-mail: drthammasorn@yahoo.com

J. CONSENT

I will be given a copy of this information form to keep.

K. PARTICIPATION IN RESEARCH IS VOLUNTARY

I am free to decline to be in this study, or to withdraw from it at any point and this will not cause any negative consequences to services I will get in the future

PARTICIPANT'S CONSENT STATEMENT

I agree to take part in the research study described here. I have read and understand the statement and I have had all my questions answered. I understand that my participation is completely voluntary.

....
Mark of Participant Date

.....
Signature of Interviewer

6.4.2 Verbal Consent Script

This is [*name of trained interviewer*] and I am now helping Dr. Thammasorn Piriyasupong from Khon Kaen Hospital to evaluate the outcomes of the antiretroviral therapy (ART) programme under Ministry of Public Health and explore factors contributing to its success. Today I would like you to give me **some** information about your family member who used to be treated in the national antiretroviral therapy programme about his/her socioeconomic status. This should take approximately about 5 minutes and can be done now. There will be no costs to me as a result of taking part in this study.

Your participation is voluntary. If you do not wish to participate, you may stop at any time. The given information will be coded (no names will be used). The code will be kept in a locked file and only Dr. Thammasorn and his co-investigators will have access to it. The code and all identifiers such as names, addresses, and phone numbers will be destroyed at

the end of the study. Therefore, no one will be able to link the samples back to me. All data are considered as strictly confidential.

You may not benefit directly from this interview, however all of the information you give may lead to a better understanding of the services available to people with the HIV/AIDS and how to improve those services in relation to antiretroviral therapy.

If you would like a copy of this letter for your records, please let me know and I will [*give you a copy now; email, mail, or fax it to you, etc.*]. If you have any questions regarding the research, please feel free to contact

Dr. Thammasorn Piriyasupong

Khon Kaen Hospital,

Khon Kaen Thailand 40000

Call: (+66) 85 0006261, (+66) 85 854 6523

E-mail: drthammasorn@yahoo.com

Again, you are free to decline to give the information at any point and this will not cause any negative consequences to services from the hospital you will get in the future

If you agree to give me the information, I will proceed to the question, if not, I will stop now

Thank you again for your help.

6.4.3 Copy of Questionnaire

Questionnaire

__/__

Questionnaire for interviewing patient under the governmental antiretroviral treatment programme

Date_____
Patient ID_____
Interviewer's name_____
Hospital name_____
Province_____
Place of interviews 1. Patient's home (with permission to visit)
2. Hospital
3. Patient's working place (with permission to visit)
4. Others, please specify

Part 1

Part 1-1: General information

1 Gender [ ]

Male=1; Female=2

2 What is your date of birth? [.../.../...]

3 What religion you are? [ ]

Buddhist=1; Christian=2; Muslim=3; Others=9

4 What is your main occupation? [ ]

Unemployed=1; Farmer or gardener=2;
Civil servant or State enterprise officer=3; Self employed=4;
General Labourer=5, House wife=6;
Others=9

If Others, please specify.....

5 Are you the main wage earner? [ ]

No=1; Yes=2.

6 How much do you approximately earn per month? [ ] Baht

7 How much does your family approximately earn per month (total income)? [ ] Baht

_____

8 What type of accommodation do you live in at the present? ☐

Owner occupied=1; Rented house=2; Rented room=3;
Live with the others, Don't have to pay=4; Vagabond=5;
Others=9

If Others, please specify.....

9 How far is it from your accommodation to the hospital? ☐ Km.

10 How long did it take for you to come to the hospital for the last visit? ...../..... Hr/min

11 How do you usually come to the hospital? ☐

On feet=1; Bicycle=2; Motorcycle=3;
Private car=4; Bus/Coach =5; Hired car=6;
Others=9

12 What is your highest education level? ☐

No formal education=1; Grade 6 (Primary school)=2;
Grade 9 or equivalent=3;
Grade 12 (Secondary school or equivalent) =4;
Diploma or equivalent=5; Bachelor degree or higher=6

13 What is your health insurance scheme? ☐

Self-pay =1; Universal Coverage (UC)=2;
Social Security=3; Civil Servant Medical Benefit Scheme=4;
Private insurance=5; Others=9

If Others, please specify.....

14 What is your present marital status? ☐

Single=1; Married=2; Separated=3;
Widow or widower=4; Divorce=5;
Not married, but live with partner=6

15 When did you know that you are HIV-infected? ...../.... mm/yy

16 Why did you go for the HIV testing? ☐

You/your spouse underwent medical treatment and had HIV testing=1;
Premarital testing=2; Testing during ANC (for you/your spouse)=3;
Voluntary testing=4; Testing for work application=5;
Testing for blood donation=6; Others=9

If Others, please specify.....

17 Are you a member of any PLHA (people living with HIV/AIDS) self-help group? ☐

No=1; Yes=2

18 How many adult (age ≥ 20) are there in your house (including you)? (sharing resources, sharing cost together with you) ☐

19 How many of these adults are infected with HIV? ☐

20 How many of these adults are currently on antiretroviral treatment? ☐

21 How many children (age<20) are there in your accommodation? ☐

If there is no child, please fill in the box with 0 and skip to question 24

22 How many of these children are HIV positive? ☐

23 How many of these children are currently on antiretroviral treatment? ☐

Part 1-2: Behaviour of antiretroviral drug taking

24 When did you start taking antiretroviral (ARV) drugs in this programme? ...../..... mm/yy

25 Have you ever take any of ARV drugs before entering to this programme? ☐

No=1; Yes=2

26 When was your last hospital visit for ARV drugs? ...../..... mm/yy

27 When will be your next hospital appointment? ...../.... mm/yy

28 What regimen of ARV are you taking now? [ ]

First-line (GPO-Vir)=1; Second-line (d4T+3TC+EFV) =2;
Third-line (d4T+3TC+IDV+RTV)=3; Others=9

If Others, please specify.....

In this following days, have you not taken ARV drugs or taken them late than 30 minutes? The interviewers please use the instruction below to ask the interviewees backward from today will 5 days ago. Use this instruction to answer question 29 and 30. (For today refers to doses in the morning only)

	Day (please specify Sun, Mon, Tue, Wed, Thu, Fri and Sat)	Number of doses you have not taken	Number of doses you have taken late than 30 minutes of usual time
Today			
Yesterday			
2 days ago			
3 days ago			
4 days ago			
5 days ago			

29 In total, how many doses have you not taken during the past 5 days? [ ] Doses

30 In total, how many doses have you taken late more than 5 days during the past 5 days? [ ] Doses

31 For the last month, how many doses you have not taken? [ ] Doses

32 For the last month, how many doses you have taken late more than 30 minutes? [ ] Doses

33 When was the last time you did not take your drugs? [ ]

Never miss any doses=1, Within last week=2;
Within last month=3; Within last 2 months=4;
Within last 3 months=5; More than 3 months=6
If the answer is =1, please skip to question 35

34 There are many reasons why people do not take their medicines. What was your main cause on the last occasion you did not take ARV drugs? [ ]

Intent not to take=1; Forgot to take=2;
Accident (e.g. drug lost)=3; Hospital ran out of drug=4;
Others=9

If Others, please specify.....

35 If you intent not to take the ARV drugs, why?
.....

Part 1-3: Health status before and after taking ARV drugs

36 Before taking the ARV drugs, were you able to work? ☐

Not able to work at all=1; Able to work but not as usual=2
Able to work as usual=3

37 Are you able to work more or less comparing with that before taking ARV drugs? ☐
Able to work less=1 No difference=2
Able to work more=3

38 Since starting the drugs, have you notice any difference in your skin? ☐
Worse=1; No difference=2;
Better=3

39 Since starting the drugs, have you notice any differences in your everyday life activities (e.g. taking a bath, eating, walking)? ☐
Worse=1; No difference=2;
Better=3.

40 Since starting the drugs, have you notice any differences in your mental health? ☐
Worse=1; No difference=2;
Better=3.

41 Do you tell your couple or your usual sex partner that you are HIV positive? (in case that your couple already died, did he/she knew that you are HIV positive before he/she died)? ☐
No=1 Yes=2
If you are single, please skip this question

42 Besides your couple, do you tell any of your family ☐
members that you are HIV positive?
No=1 Yes=2

43 Do you tell your neighbours or people in your community that you are HIV positive? ☐
No=1 Yes=2

44 In any occasions, have you been turned away by your neighbours or the others because of HIV (e.g. walk away; refuse to have meal with you)? ☐
Never =1, Yes=2, Not sure =3
Neighbours and community do not know =4
If the answer is =1 or =3 or =4 please skip to question 46

45 If you have been turned away, do your neighbours and community accept you more or less after taking the ARV drugs? ☐

Accept less=1 No difference=2; Accept more=3;
Not sure =4

46 During the past 3 months, did you still have sex? ☐

No=1; Yes=2
If the answer is =1, please skip to question 49

47 During the past 3 months, how many people did you have sex with? ☐

48 During the past 3 months, how often did you use condom? ☐

Never=1 Sometimes=2 Usually =3 Always =4

49 After taking the medicine, some people have sex more often but some don't, in your case do you have sex more or less often compare with before you taking the medicine? ☐

Less often=1; No difference=2; More often=3;
Never had sex since starting ART=4

Part 1-4: ART service and follow up system

50 How much time do you usually spend at the ARV clinic (including related activities with the ART)? ..../.... Hr/min

51 How do you feel about amount of time you usually spend at the ARV clinic? ☐

Too short=1; Appropriate =2; Too long=3

52 Did you see the doctor for your last hospital visit for the ARV drugs? ☐

No=1; Yes=2

53 For the last time you saw the doctor, how much time did you spend with the doctor? ☐ Minutes

54 How did you feel about time you spent with the doctor? ☐

Too short=1; Appropriate =2; Too long=3;

55 Have you been informed about benefit, harm and adverse effects of the ARV drugs by hospital staff?
No=1; Yes=2
if the answer is =1, please skip to question 57

56 How did you understand the information they gave you?

Not understood=1; Partly understood =2;
Well understood =3

57 Do you feel private enough at the ARV clinic?

No=1; Yes=2

58 Have you conceived of dislike by hospital staff?

Never=1; Yes, sometime=2,
Yes, always=3 Not sure=4

59 What method do you use for reminding to take medicine at the correct time?

.....

60 In last 3 months, have you ever missed any of hospital appointment?
No=1; Yes=2
If the answer is =1, please skip to 64

61 If yes, why
.....
.....

62 What did the hospital do when you missed the last

appointment?
Did nothing=1; Mailed you =2; Called you=3; Sent someone to visit=4;
Others=9;

If Others, please specify.....

63 And what did you do when you realized that you missed the appointment?
Went to hospital as soon as possible=1;
Went to hospital in my own free time=2;
Went to hospital for the next visit=3; Others=9

If Others, please specify.....

Part 1-5: Adverse effect of ARV drugs

64 Have you ever had any adverse effects that made you feel unwell? ☐
No=1; Yes, minor side effect and able work=2;
Yes, and unable to do anything at all=3
if the answer is =1, please skip to question 67

65 Did you stop taking the medicine during the adverse effect occurred? ☐
No=1; Yes=2

66 If you have the adverse effect from the drug, who is usually the **first one** you will ask for help? ☐
Hospital staff=1; Family members =2; Other PLHA=3;
NGO=4, Others=9

If Others, please specify.....

Part 1-6: Reported satisfaction

67 How long do you expect to keep on taking the drug? ☐
As long as possible =1; Will quit soon=2; Until the doctor stop prescribing=4 Others=9

If Others, please specify.....

68 What do you expect from the program?
.....

69 In overall, do you feel satisfied with the antiretroviral programme delivered by the hospital? ☐
Very dissatisfied=1; Generally dissatisfied =2;
Generally satisfied=3; Very satisfied=4

70 Do you feel satisfied with the convenient of the ARV clinic? ☐
Very dissatisfied=1; Generally dissatisfied =2;
Generally satisfied=3; Very satisfied=4

71 Do you feel satisfied with the explanation of service procedure at ARV clinic? ☐
Very dissatisfied=1; Generally dissatisfied =2;
Generally satisfied=3; Very satisfied=4

72 Do you feel satisfied with the knowledge of the clinic ☐

staff?
Very dissatisfied=1; Generally dissatisfied =2;
Generally satisfied=3; Very satisfied=4

73 Do you feel satisfied with the ARV clinic staff interest and enthusiasm?
Very dissatisfied=1; Generally dissatisfied =2;
Generally satisfied=3; Very satisfied=4

74 Could you please give any suggestion for hospital to improve quality of ATC programme?
.....

75 Will you recommend any of your relative to come to this hospital?
No=1; Yes=2

Part 2: Health-related quality of life

HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE

Date_____
Patient ID_____
Interviewer_____
Hospital_____

Instructions for interviews

The questions in this questionnaire begin with a statement followed by two opposite answers. Numbers extend from one extreme answer to its opposite.
Please circle the number between 1 and 5 which is most true for you. There are no right or wrong answers. Completely honest answers will be most helpful.

EXAMPLE: I am hungry:

Not at all				Extremely
1	2	3	4	5

- If you are not even a little bit hungry, you might circle 1.
- If you are a little hungry, you might circle a 2.
- If you are feeling moderately hungry, you might circle a 3.
- If you are very hungry, you might circle a 4.
- If you are extremely hungry, you might circle 5.

PART 2-1: OVERALL HEALTH STATUS

1) Considering all parts of your life - physical, emotional, social, spiritual, and financial - over the past two (2) days the quality of my life has been:

Very bad				Excellent
1	2	3	4	5

2) And considering all parts of your life- physical, emotional, social, spiritual, and financial- comparing to just before taking ARV drugs you life has been

Extremely worse				Extremely better
1	2	3	4	5

PART 2-2: PHYSICAL SYMPTOMS OR PHYSICAL PROBLEMS

(1) For the questions in Part 2, please list the PHYSICAL SYMPTOMS OR PROBLEMS which have been the biggest problem for you over the past two (2) days. (Some examples are: pain, tiredness, weakness, nausea, vomiting, constipation, diarrhoea, trouble sleeping, shortness of breath, lack of appetite, sweating, immobility. Feel free to refer to others if necessary)
(2) Circle the number which best shows how big a problem each one has been for you OVER THE PAST TWO (2) DAYS.
(3) If, over the past two (2) days, you had NO physical symptoms or problems, or only one or two,

answer for each of the ones you have had and write "none" for the extra questions in Part B, then continue with Part C.

3) Over the past two (2) days, one troublesome symptom has been:_____
(write symptom)

Magnitude of problem
No problem Tremendous
1 2 3 4 5

4) Over the past two (2) days, another troublesome symptom has been:_____
(write symptom)

Magnitude of problem
No problem Tremendous
1 2 3 4 5

5) Over the past two (2) days, a third troublesome symptom has been:_____
(write symptom)

Magnitude of problem
No problem Tremendous
1 2 3 4 5

6) Over the past two (2) days I have felt that my physical is
Extremely weak Very well
1 2 3 4 5

PART 2-3: PSYCHO-SOCIAL STATUS

Please choose the number which best describes your feelings and thoughts OVER THE PAST TWO (2) DAYS.

7) Over the past two (2) days, I have been depressed:
Not at all Extremely
1 2 3 4 5

8) Over the past two (2) days, I have been nervous or worried:
Not at all Extremely
1 2 3 4 5

9) Over the past two (2) days, how much of the time did you feel sad?
Never Always
1 2 3 4 5

10) Over the past two (2) days, when I thought of the future, I was:
Not afraid Terrified
1 2 3 4 5

11) Over the past two (2) days, my life has been:
Utterly meaningless and without purpose Purposeful and meaningful
1 2 3 4 5

12) Over the past two (2) days, when I thought about my whole life, I felt that in achieving life goals I have:
Made no Progressed

Progress whatsoever				to complete fulfilment
1	2	3	4	5

13) Over the past two (2) days, when I thought about my life, I felt that my life to this point has been:

Completely worthless				Very worthwhile
1	2	3	4	5

14) Over the past two (2) days, I have felt that I have:

No control over my life				Complete control over my life
1	2	3	4	5

15) Over the past two (2) days, I felt good about myself as a person.

Completely disagree				Completely agree
1	2	3	4	5

16) To me, the past two (2) days were:

Burden				A gift
1	2	3	4	5

17) Over the past two (2) days, the world has been:

An impersonal unfeeling place				Caring and responsive to my needs
1	2	3	4	5

18) Over the past two (2) days, I have felt supported:

Not at all				Completely
1	2	3	4	5

PART2- 4: EQ-5D

Please make "X" mark in the square which indicate you health status the most for today

MOBILITY

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

SELF-CARE

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework family or leisure activities)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

PAIN/DISCOMFORT

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

ANXIETY/DEPRESSION

I am not anxious or depressed ☐

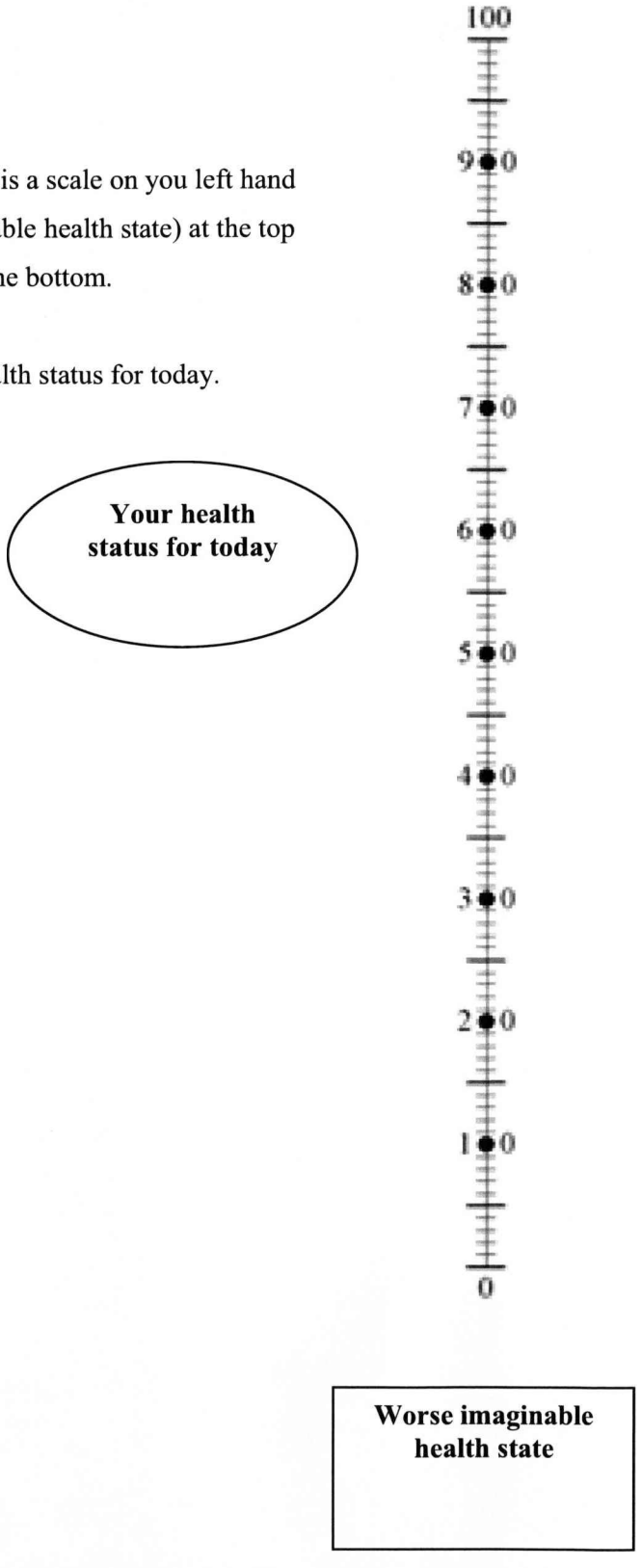
I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

PART 2-5: VAS

For evaluating of you health status, there is a scale on you left hand which has endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

Please mark on the scale to state your health status for today.



6.5 Annex 5: Alternative method to calculate the sample size

The alternative method to calculation the sample size for the present study is to use the SSP programme which involved two groups with a survival outcome. It is assumed that the patients had an exponential survival distribution. Each patient was followed until either the event occurs in that person, the person was lost to follow-up or administratively censored, or the study was terminated. It allowed to specify the distribution of patient recruitment, whether they enter the study uniformly or non-uniformly. Specifically, non-uniform entry followed a truncated exponential distribution. The methods of Lachin & Foulkes (1986) are implemented for the calculations. From this calculation, the sample was required to be not fewer than 456 which in this presented study, we included 501 participants. Description and value of each parameter to be put in the programme were shown in Table below

Table 6-9: Values of parameters used in the alternative method for sample size calculation

Parameters	Definition	Expected value
Power	The probability of rejecting the null hypothesis given the alternative hypothesis is true. It is a value between 0 and 1, though common values include 0.80 and 0.90	0.8
Ration of sample size, control: treated	The ratio of the sample size in the control group to the sample size in the treated group. Examples: for equal sample size, enter 1. For a 3:1 control:treated ratio, enter 3. In general, if R=n/m, then the total sample size N is n(R+1)/R, where n and m are the sample sizes of the control and treated groups, respectively.	1
Control survival rate	The expected cumulative proportion surviving at the end of the study in the control group. A value greater than or equal to 0 and less than or equal to 1 must be entered	0.8
Relative risk, treated:control	The relative risk of the treated group compared to the control group. A value greater than 0 must be entered.	2
Length of accrual period	The number of time periods required to recruit all of the patients into the study. It must be a value greater than 0, usually expressed as months or years.	6
Minimum follow-up time	The number of periods of follow-up that the last patient recruited must have. Hence, the length of the entire study is the sum of the length of accrual period and minimum follow-up time. The exponential hazard rates are calculated based on the sum of these two values. This must have the same unit of time as the length of the accrual period.	3
Two-sided Type I error	The probability of rejecting the null hypothesis given the null hypothesis is true. It must be a value greater than 0 and less than 1, though common values include 0.01 and 0.05.	0.05
Non-uniform accrual parameter	This specifies the distribution of the patients being recruited into the study. Valid values are between –10 and 10. A value of 0 implies a uniform distribution. Otherwise, a truncated exponential distribution is assumed: negative values imply that more patients are recruited later in the accrual period, whereas positive values imply that more patients are recruited early in the accrual period. For example, -9 implies that almost all of the patients are recruited at the end of the accrual period, and 2 implies that slightly more patients are recruited early in accrual period.	0
Control loss to follow-up rate	The expected cumulative proportions at which those in the control and treated groups are lost to follow-up by the end of the study. Different rates for each group is allowed. It is assumed that these losses are distributed exponentially. Values must be greater-than or equal to 0 and less than 1.	0.1
Treated loss to follow-up rate		0.1
Rate of crossover to treated	The expected cumulative proportion of patients who cross over to the treatment assigned to the other group. It is assumed that the drop-ins and drop-outs are subject to the same hazard rate for the treated and control groups, respectively, from enrolment until the end of the follow-up period.	0.1
Rate of crossover to control		0.1
Total sample size		**456**

7 References

(2000). *Highly active antiretroviral therapy including protease inhibitors does not confer a unique CD4 cell benefit. The AVANTI and INCAS Study Groups*. Aids 14(10): 1383-8.

Abadia-Barrero, C. E. and Castro, A. (2006). *Experiences of stigma and access to HAART in children and adolescents living with HIV/AIDS in Brazil*. Social Science & Medicine 62(5): 1219-28.

Abdool-Karim, S. S., Abdool-Karim, Q., Friedland, G., Lalloo, U. and El-Sadr, W. M. (2004). *Implementing antiretroviral therapy in resource-constrained settings: opportunities and challenges in integrating HIV and tuberculosis care*. AIDS 18(7): 975-9.

Aboulker, J. P., Babiker, A., Chaix, M. L., Compagnucci, A., Darbyshire, J., Debre, M., Faye, A., Giaquinto, C., Gibb, D. M., Harper, L., Saidi, Y. and Walker, A. S. (2004). *Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome*. AIDS 18(2): 237-45.

Aceijas, C., Oppenheimer, E., Stimson, G. V., Ashcroft, R. E., Matic, S. and Hickman, M. (2006). *Antiretroviral treatment for injecting drug users in developing and transitional countries 1 year before the end of the "Treating 3 million by 2005. Making it happen. The WHO strategy" ("3 by 5")*. Addiction 101(9): 1246-53.

Ahdieh Grant, L., Silverberg, M. J., Palacio, H., Minkoff, H., Anastos, K., Young, M. A., Nowicki, M., Kovacs, A., Cohen, M. and Munoz, A. (2001). *Discontinuation of potent antiretroviral therapy: predictive value of and impact on CD4 cell counts and HIV RNA levels*. AIDS 15(16): 2101-8.

Ahmad, K. (2002). *Thailand court forces reversal of drug firm antiretroviral patent.* Lancet 360(9341): 1231.

Alfonso, V., Bermbach, N., Geller, J. and Montaner, J. S. (2006). *Individual variability in barriers affecting people's decision to take HAART: a qualitative study identifying barriers to being on HAART.* AIDS Patient Care and STDS 20(12): 848-57.

Alfonso, V., Geller, J., Bermbach, N., Drummond, A. and Montaner, J. S. (2006). *Becoming a "treatment success": what helps and what hinders patients from achieving and sustaining undetectable viral loads.* AIDS Patient Care and STDS 20(5): 326-34.

Allardice, G. M., McMenamin, J. J., Parpia, T., Gibbs, J., McSharry, C. and Whitelaw, J. (1998). *The recent impact of antiretroviral combination therapy on CD4 counts, AIDS and death in HIV-infected persons: routine HIV surveillance in Scotland.* International Journal of STDs & AIDS 9(10): 561-6.

Ammassari, A., Antinori, A., Cozzi-Lepri, A., Trotta, M. P., Nasti, G., Ridolfo, A. L., Mazzotta, F., Wu, A. W., d'Arminio Monforte, A. and Galli, M. (2002). *Relationship between HAART adherence and adipose tissue alterations.* Journal of Acquired Immune Deficiency Syndrome 31 Suppl 3: S140-4.

Amundsen, E. J. and Fekjaer, H. (2003). *Progression to AIDS slowed even more after the first two years with highly active antiretroviral therapy.* Scandinavian Journal of Public Health 31(4): 312-8.

Ana Revenga, Mead Over, Emiko Masaki, Wiwat Peerapatanapokin, Julian Gold, Viroj Tangchareonsathien and Thanprasertsuk, S. (2006). *The economics of*

effective AIDS treatment: Evaluating policy options for Thailand, The international bank for reconstruction and development/ The World Bank.

Anastos, K., Gange, S. J., Lau, B., Weiser, B., Detels, R., Giorgi, J. V., Margolick, J. B., Cohen, M., Phair, J., Melnick, S., Rinaldo, C. R., Kovacs, A., Levine, A., Landesman, S., Young, M., Munoz, A. and Greenblatt, R. M. (2000). *Association of race and gender with HIV-1 RNA levels and immunologic progression*. Journal of Acquired Immune Deficiency Syndrome 24(3): 218-26.

Andersen, R., Bozzette, S., Shapiro, M., St Clair, P., Morton, S., Crystal, S., Goldman, D., Wenger, N., Gifford, A., Leibowitz, A., Asch, S., Berry, S., Nakazono, T., Heslin, K. and Cunningham, W. (2000). *Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS Consortium. HIV Cost and Services Utilization Study*. Health Services Research 35(2): 389-416.

Anderson, K. H. and Mitchell, J. M. (2000). *Differential access in the receipt of antiretroviral drugs for the treatment of AIDS and its implications for survival*. Archives of Internal Medicine 160(20): 3114-20.

Anis, A. H., Guh, D., Hogg, R. S., Wang, X. H., Yip, B., Craib, K. J., O'Shaughnessy, M. V., Schechter, M. T. and Montaner, J. S. (2000). *The cost effectiveness of antiretroviral regimens for the treatment of HIV/AIDS*. Pharmacoeconomics 18(4): 393-404.

Arpinelli, F., Visona, G., Bruno, R., De Carli, G. and Apolone, G. (2000). *Health-related quality of life in asymptomatic patients with HIV. Evaluation of the SF-36 health survey in Italian patients*. Pharmacoeconomics 18(1): 63-72.

Aurpibul, L., Puthanakit, T., Lee, B., Mangklabruks, A., Sirisanthana, T. and Sirisanthana, V. (2007). *Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy*. Antiviral Therapy 12(8): 1247-54.

Badri, M., Bekker, L. G., Orrell, C., Pitt, J., Cilliers, F. and Wood, R. (2004). *Initiating highly active antiretroviral therapy in sub-Saharan Africa: an assessment of the revised World Health Organization scaling-up guidelines*. AIDS 18(8): 1159-68.

Bailey, J. E., Van Brunt, D. L., Raffanti, S. P., Long, W. J. and Jenkins, P. H. (2003). *Improvements in access to care for HIV and AIDS in a statewide Medicaid managed care system*. American Journal of Managed Care 9(9): 595-602.

Bailey, J. E., Van Brunt, D. L., Somes, G. W., Dorko, C. S. and Wan, J. Y. (2004). *Impact of a statewide Medicaid managed care system on healthcare utilization and outcomes for people living with HIV*. American Journal of Medical Science 328(6): 305-14.

Baker, R. (1998). *Short-course AZT reduces HIV transmission to infants; Glaxo cuts AZT price for developing countries*. Beta: 7.

Barron, Y., Cole, S. R., Greenblatt, R. M., Cohen, M. H., Anastos, K., DeHovitz, J. A., Delapenha, R. and Gange, S. J. (2004). *Effect of discontinuing antiretroviral therapy on survival of women initiated on highly active antiretroviral therapy*. AIDS 18(11): 1579-84.

Bazian (2005). *Do nurse practitioners provide equivalent care to doctors as a first point of contact for patients with undifferentiated medical problems?* Evidence Based Healthcare and Public Health 9: 179-191.

Bedell, R., Heath, K., Hogg, R., Wood, E., Press, N. and Yip, B. (2003). *Total lymphocyte count as a possible surrogate of CD4 cell count to prioritize eligibility for antiretroviral therapy among HIV-infected individuals in resource-limited settings*. Antiviral Therapy 8(5): 379-384.

Behjati, S. (2006). *Could 3 by 5 increase HIV transmission?* Lancet 367(9508): 396.

Bennett, S. and Chanfreau, C. (2005). *Approaches to rationing antiretroviral treatment: ethical and equity implications*. Bulletin of the World Health Organisation 83(7): 541-7.

Beusterien, K. M., Davis, E. A., Flood, R., Howard, K. and Jordan, J. (2008). *HIV patient insight on adhering to medication: a qualitative analysis*. AIDS Care 20(2): 244-52.

Bhattacharya, J., Goldman, D. and Sood, N. (2003). *The link between public and private insurance and HIV-related mortality*. Journal of Health Economics 22(6): 1105-22.

Birch, S. and Gafni, A. (1992). *Cost-effectiveness/utility analyses. Do current decision rules lead us to where we want to be?* Journal of Health Economics 22(6): 1105-1122.

Bogaards, J. A., Weverling, G. J., Geskus, R. B., Miedema, F., Lange, J. M., Bossuyt, P. M. and Goudsmit, J. (2003). *Low versus high CD4 cell count as starting point for introduction of antiretroviral treatment in resource-poor settings: a scenario-based analysis*. Antiviral Therapy 8(1): 43-50.

Bonnet, F., Morlat, P., Chene, G., Mercie, P., Neau, D., Chossat, I., Decoin, M., Djossou, F., Beylot, J. and Dabis, F. (2002). *Causes of death among HIV-infected patients in the era of highly active antiretroviral therapy, Bordeaux, France, 1998-1999*. HIV Medicine 3(3): 195-9.

Bouhnik, A. D., Chesney, M., Carrieri, P., Gallais, H., Moreau, J., Moatti, J. P., Obadia, Y. and Spire, B. (2002). *Nonadherence among HIV-infected injecting drug users: the impact of social instability*. Journal of Acquired Immune Deficiency Syndrome 31 Suppl 3: S149-53.

Bozzette, S. A., Joyce, G., McCaffrey, D. F., Leibowitz, A. A., Morton, S. C., Berry, S. H., Rastegar, A., Timberlake, D., Shapiro, M. F. and Goldman, D. P. (2001). *Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy*. N Engl J Med 344(11): 817-23.

Bozzette, S. A., Kanouse, D. E., Berry, S. and Duan, N. (1995). *Health status and function with zidovudine or zalcitabine as initial therapy for AIDS. A randomized controlled trial. Roche 3300/ACTG 114 Study Group*. Journal of the American Medical Association 273(4): 295-301.

Braitstein, P., Brinkhof, M. W., Dabis, F., Schechter, M., Boulle, A., Miotti, P., Wood, R., Laurent, C., Sprinz, E., Seyler, C., Bangsberg, D. R., Balestre, E., Sterne, J. A., May, M. and Egger, M. (2006). *Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries*. Lancet 367(9513): 817-24.

Brown, D. M., Thorne, J. E., Foster, G. L., Duncan, J. L., Brune, L. M., Munana, A., Meinert, C. L. and Jabs, D. A. (2006). *Factors affecting attrition in a longitudinal study of patients with AIDS*. AIDS Care 18(7): 821-9.

Brown, S. A. and Grimes, D. E. (1995). *A meta-analysis of nurse practitioners and nurse midwives in primary care*. Nurs Res 44(6): 332-9.

Brown, T. and Peerapatanapokin, W. (2004). *The Asian Epidemic Model: a process model for exploring HIV policy and programme alternatives in Asia*. Sex Transm Infect 80 Suppl 1: i19-24.

Bucciardini, R., Murri, R., Guarinieri, M., Starace, F., Martini, M., Vatrella, A., Cafaro, L., Fantoni, M., Grisetti, R., Monforte, A., Fragola, V., Arcieri, R., Del Borgo, C., Tramarin, A., Massella, M., Lorenzetti, D. and Vella, S. (2006). *ISSQoL: a new questionnaire for evaluating the quality of life of people living with HIV in the HAART era.* Quality of Life Research 15(3): 377-90.

Buckingham, R. W., Meister, E. and Webb, N. (2004). *Condom use among the female sex worker population in Thailand.* International Journal of STDs & AIDS 15(3): 210-1.

Burgoyne, R. and Renwick, R. (2004). *Social support and quality of life over time among adults living with HIV in the HAART era.* Soc Sci Med 58(7): 1353-66.

Burgoyne, R. W., Rourke, S. B., Behrens, D. M. and Salit, I. E. (2004). *Long-term quality-of-life outcomes among adults living with HIV in the HAART era: the interplay of changes in clinical factors and symptom profile.* AIDS Behavior 8(2): 151-63.

Burman, W. J., Grund, B., Roediger, M. P., Friedland, G., Darbyshire, J. and Wu, A. W. (2008). *The impact of episodic CD4 cell count-guided antiretroviral therapy on quality of life.* J Acquir Immune Defic Syndr 47(2): 185-93.

Butler, K. M., Husson, R. N., Lewis, L. L., Mueller, B. U., Venzon, D. and Pizzo, P. A. (1992). *CD4 status and P24 antigenemia. Are they useful predictors of survival in HIV-infected children receiving antiretroviral therapy?* American Journal of Diseases in Childhood 146(8): 932-6.

Byrne, M. W. and Honig, J. (2005). *Psychometrics of Child Health Questionnaire parent short form (CHQ-28) used to measure quality of life in HIV-infected children on complex anti-retroviral therapy*. Qual Life Res 14(7): 1769-74.

Byrne, M. W. and Honig, J. (2006). *Health-related quality of life of HIV-infected children on complex antiretroviral therapy at home*. Journal of the Association of Nurses in AIDS Care 17(2): 27-35.

Caine, N., Sharples, L. D., Hollingworth, W., French, J., Keogan, M., Exley, A., Hodgkins, D. and Bilton, D. (2002). *A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic*. Health Technol Assess 6(27): 1-71.

Canestri, A., Sow, P. S., Vray, M., Ngom, F., M'Boup, S., Kane, C. T., Delaporte, E., Gueye, M., Peytavin, G., Girard, P. M. and Landman, R. (2007). *Poor efficacy and tolerability of stavudine, didanosine, and efavirenz-based regimen in treatment-naive patients in Senegal*. MedGenMed 9(4): 7.

Carrieri, M. P., Chesney, M. A., Spire, B., Loundou, A., Sobel, A., Lepeu, G. and Moatti, J. P. (2003). *Failure to maintain adherence to HAART in a cohort of French HIV-positive injecting drug users*. International Journal of Behavioural Medicine 10(1): 1-14.

Carrieri, P., Spire, B., Duran, S., Katlama, C., Peyramond, D., Francois, C., Chene, G., Lang, J. M., Moatti, J. P. and Leport, C. (2003). *Health-related quality of life after 1 year of highly active antiretroviral therapy*. J Acquir Immune Defic Syndr 32(1): 38-47.

Celentano, D. D., Galai, N., Sethi, A. K., Shah, N. G., Strathdee, S. A., Vlahov, D. and Gallant, J. E. (2001). *Time to initiating highly active antiretroviral therapy among HIV-infected injection drug users*. AIDS 15(13): 1707-15.

Chaisson, R. E., Keruly, J. C. and Moore, R. D. (1995). *Race, sex, drug use, and progression of human immunodeficiency virus disease*. N Engl J Med 333(12): 751-6.

Chaiwarith, R., Wachirakaphan, C., Kotarathititum, W., Praparatanaphan, J., Sirisanthana, T. and Supparatpinyo, K. (2007). *Sensitivity and specificity of using CD4+ measurement and clinical evaluation to determine antiretroviral treatment failure in Thailand.* Int J Infect Dis 11(5): 413-6.

Chariyalertsak, S., Oberdorfer, P., Suwanteerangkul, J., Sarna, A., Guest, P. and Wu, A. (2006). Improved socioeconomic status and quality of life, and decreased hospitalization rates among patients in Thailand one year after initiating HAART

Chasombat, S., Lertpiriyasuwat, C., Thanprasertsuk, S., Suebsaeng, L. and Lo, Y. R. (2006). *The National Access to Antiretroviral Program for PHA (NAPHA) in Thailand.* Southest Asian Journal of Tropical Medicine and Public Health 37(4): 704-15.

Chasombat, S., Lertpiriyasuwat, C., Thanprasertsuk, S., Suebsaeng, L. and Lo, Y. R. (2006). *The National Access to Antiretroviral Program for PHA (NAPHA) in Thailand.* Southeast Asian J Trop Med Public Health 37(4): 704-15.

Chen, R. Y., Westfall, A. O., Mugavero, M. J., Cloud, G. A., Raper, J. L., Chatham, A. G., Acosta, E. P., Taylor, K. H., Carter, J. and Saag, M. S. (2003). *Duration of highly active antiretroviral therapy regimens*. Clinical Infectious Diseases 37(5): 714-22.

Chene, G., Binquet, C., Moreau, J. F., Neau, D., Pellegrin, I., Malvy, D., Ceccaldi, J., Lacoste, D. and Dabis, F. (1998). *Changes in CD4+ cell count and the risk of opportunistic infection or death after highly active antiretroviral*

treatment. Groupe d'Epidemiologie Clinique du SIDA en Aquitaine. AIDS 12(17): 2313-20.

Chesney, M. A. (2000). *Factors affecting adherence to antiretroviral therapy*. Clinical Infectious Diseases 30 Suppl 2: S171-6.

Chinnock, P., Siegfried, N. and Clarke, M. (2005). *Is evidence-based medicine relevant to the developing world?* PLoS Medicine 2(5): e107.

Clarke, S., Delamere, S., McCullough, L., Hopkins, S., Bergin, C. and Mulcahy, F. (2003). *Assessing limiting factors to the acceptance of antiretroviral therapy in a large cohort of injecting drug users*. HIV Medicine 4(1): 33-7.

Clarke, S. M. and Mulcahy, F. M. (2000). *Antiretroviral therapy for drug users*. International Journal of STDs & AIDS 11(10): 627-31.

Cohen, S. R., Hassan, S. A., Lapointe, B. J. and Mount, B. M. (1996). *Quality of life in HIV disease as measured by the McGill quality of life questionnaire*. AIDS 10(12): 1421-7.

Collier, A., Conway, B., Markowit, M., Hecht, F., Walker, B., Connick, E., Apuzzo, L., Vaida, F., Gallant, J., Ernstrom, K., Little, S., Routy, J.-P. and Margolick, J. (2009). Tolerability and Efficacy of PI Versus NNRTI-Based Regimens in Subjects Receiving HAART During Acute or Early HIV Infection. *Journal of Acquired Immune Deficiency Syndromes*. 50**:** 267-275.

Conference, W. M. (2001). *WTO Ministernal Conference. Declaration on the TRIPS Agreement and Public Health*

Cooper, V., Buick, D., Horne, R., Lambert, N., Gellaitry, G., Leake, H. and Fisher, M. (2002). *Perceptions of HAART among gay men who declined a treatment offer: preliminary results from an interview-based study*. AIDS Care 14(3): 319-28.

Creese, A., Floyd, K., Alban, A. and Guinness, L. (2002). *Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence.* Lancet 359(9318): 1635-43.

Crepaz, N., Hart, T. A. and Marks, G. (2004). *Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review.* Journal of the American Medical Assocation 292(2): 224-36.

Cruess, D. G., Douglas, S. D., Petitto, J. M., Have, T. T., Gettes, D., Dube, B., Cary, M. and Evans, D. L. (2005). *Association of resolution of major depression with increased natural killer cell activity among HIV-seropositive women.* American Journal of Psychiatry 162(11): 2125-30.

Cullum, N., Spilsbury, K. and Richardson, G. (2005). *Nurse led care.* British Medical Journal 330(7493): 682-3.

Cunningham, W. E., Markson, L. E., Andersen, R. M., Crystal, S. H., Fleishman, J. A., Golin, C., Gifford, A., Liu, H. H., Nakazono, T. T., Morton, S., Bozzette, S. A., Shapiro, M. F. and Wenger, N. S. (2000). *Prevalence and predictors of highly active antiretroviral therapy use in patients with HIV infection in the united states. HCSUS Consortium. HIV Cost and Services Utilization.* Journal of Acquired Immune Deficiency Syndrome 25(2): 115-23.

d'Arminio Monforte, A., Lepri, A. C., Rezza, G., Pezzotti, P., Antinori, A., Phillips, A. N., Angarano, G., Colangeli, V., De Luca, A., Ippolito, G., Caggese, L., Soscia, F., Filice, G., Gritti, F., Narciso, P., Tirelli, U. and Moroni, M. (2000). *Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients.* AIDS 14(5): 499-507.

DeHovitz, J., Kovacs, A., Feldman, J., Anastos, K., Young, M., Cohen, M., Gange, S., Melnick, S. and Greenblatt, R. (2000). *The relationship between virus load response to highly active antiretroviral therapy and change in CD4 cell counts: A report from the Women's interagency HIV study*. Journal of Infectious Diseases 182(5): 1527-1530.

Delate, T. and Coons, S. J. (2001). *The use of 2 health-related quality-of-life measures in a sample of persons infected with human immunodeficiency virus*. Clinical Infectious Diseases 32(3): E47-52.

Desclaux, A., Ciss, M., Taverne, B., Sow, P. S., Egrot, M., Faye, M. A., Laniece, I., Sylla, O., Delaporte, E. and Ndoye, I. (2003). *Access to antiretroviral drugs and AIDS management in Senegal*. AIDS 17 Suppl 3: S95-101.

Diabate, S., Alary, M. and Koffi, C. K. (2007). *Determinants of adherence to highly active antiretroviral therapy among HIV-1-infected patients in Cote d'Ivoire*. AIDS 21(13): 1799-803.

Djomand, G., Roels, T., Ellerbrock, T., Hanson, D., Diomande, F., Monga, B., Maurice, C., Nkengasong, J., Konan-Koko, R., Kadio, A., Wiktor, S., Lackritz, E., Saba, J. and Chorba, T. (2003). *Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire*. AIDS 17 Suppl 3: S5-15.

Dorrucci, M., Pezzotti, P., Grisorio, B., Minardi, C., Muro, M. S., Vullo, V. and Monforte, A. (2001). *Time to discontinuation of the first highly active antiretroviral therapy regimen: a comparison between protease inhibitor- and non-nucleoside reverse transcriptase inhibitor-containing regimens*. AIDS 15(13): 1733-6.

Dray-Spira, R. and Lert, F. (2003). *Social health inequalities during the course of chronic HIV disease in the era of highly active antiretroviral therapy*. AIDS 17(3): 283-90.

Duncombe, C., Kerr, S. J., Ruxrungtham, K., Dore, G. J., Law, M. G., Emery, S., Lange, J. M., Phanuphak, P. and Cooper, D. A. (2005). *HIV disease progression in a patient cohort treated via a clinical research network in a resource limited setting*. AIDS 19(2): 169-78.

Easterbrook, P. J., Keruly, J. C., Creagh-Kirk, T., Richman, D. D., Chaisson, R. E. and Moore, R. D. (1991). *Racial and ethnic differences in outcome in zidovudine-treated patients with advanced HIV disease. Zidovudine Epidemiology Study Group*. Journal of the American Medical Association 266(19): 2713-8.

Enanoria, W. T., Ng, C., Saha, S. R. and Colford Jr, J. M. (2004). *Treatment outcomes after highly active antiretroviral therapy: a meta-analysis of randomised controlled trials*. Lancet Infectious Diseases 4(7): 414-25.

Erhabor, O., Uko, E. K. and Adias, T. (2006). *Absolute lymphocyte count as a marker for CD4 T-lymphocyte count: criterion for initiating antiretroviral therapy in HIV infected Nigerians*. Nigerian Journal of Medicine 15(1): 56-9.

Fang, C. T., Hsu, H. M., Twu, S. J., Chen, M. Y., Chang, Y. Y., Hwang, J. S., Wang, J. D. and Chuang, C. Y. (2004). *Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan*. Journal of Infectious Disease 190(5): 879-85.

Farmer, P., Leandre, F., Mukherjee, J. S., Claude, M., Nevil, P., Smith-Fawzi, M. C., Koenig, S. P., Castro, A., Becerra, M. C., Sachs, J., Attaran, A. and Kim,

J. Y. (2001). *Community-based approaches to HIV treatment in resource-poor settings*. Lancet 358(9279): 404-9.

Fassinou, P., Elenga, N., Rouet, F., Laguide, R., Kouakoussui, K. A., Timite, M., Blanche, S. and Msellati, P. (2004). *Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Cote d'Ivoire*. AIDS 18(14): 1905-13.

Fiscella, K., Franks, P., Gold, M. R. and Clancy, C. M. (2000). *Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care*. Journal of the American Medical Association 283(19): 2579-84.

Fischl, M. A., Richman, D. D., Grieco, M. H., Gottlieb, M. S., Volberding, P. A., Laskin, O. L., Leedom, J. M., Groopman, J. E., Mildvan, D., Schooley, R. T. and et al. (1987). *The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial*. New England Journal of Medicine 317(4): 185-91.

Fitzsimmons, D., Hawker, S. E., Simmonds, P., George, S. L., Johnson, C. D. and Corner, J. L. (2005). *Nurse-led models of chemotherapy care: mixed economy or nurse-doctor substitution?* Journal of Advanced Nursing 50(3): 244-52.

Ford, N., Wilson, D., Bunjumnong, O. and von Schoen Angerer, T. (2004). *The role of civil society in protecting public health over commercial interests: lessons from Thailand*. Lancet 363(9408): 560-3.

Freedberg, K. A., Losina, E., Weinstein, M. C., Paltiel, A. D., Cohen, C. J., Seage, G. R., Craven, D. E., Zhang, H., Kimmel, A. D. and Goldie, S. J. (2001). *The cost effectiveness of combination antiretroviral therapy for HIV disease*. New England Journal of Medicine 344(11): 824-31.

Gadelha, A. J., Accacio, N., Costa, R. L., Galhardo, M. C., Cotrim, M. R., de Souza, R. V., Morgado, M., Marzochi, K., Lourenco, M. C. and Rolla, V. C. (2002). *Morbidity and survival in advanced AIDS in Rio de Janeiro, Brazil*. Rev Inst Med Trop Sao Paulo 44(4): 179-86.

Galai, N., Vlahov, D., Bareta, J. C., Wang, C., Cohn, S. and Sterling, T. R. (2005). *Prognostic factors for survival differ according to CD4+ cell count among HIV-infected injection drug users: pre-HAART and HAART eras*. Journal of Acquired Immune Deficiency Syndrome 38(1): 74-81.

Garcia Ordonez, M. A., Mansilla Francisco, J. J., Nieto Aragon, E., Cereto, M. R., Salas Samper, F., Vallejo Diaz, M. and Martinez Gonzalez, J. (2001). *[Quality of life associated with the health of patients with HIV infection measured with the Health Questionnaire SF-36]*. Annals of Medicine Internationale 18(2): 74-9.

Garner, P., Kale, R., Dickson, R., Dans, T. and Salinas, R. (1998). *Getting research findings into practice: implementing research findings in developing countries*. British Medical Journal 317(7157): 531-5.

Garner, P., Meremikwu, M., Volmink, J., Xu, Q. and Smith, H. (2004). *Putting evidence into practice: how middle and low income countries "get it together"*. British Medical Journal 329(7473): 1036-9.

Gebo, K. A., Chaisson, R. E., Folkemer, J. G., Bartlett, J. G. and Moore, R. D. (1999). *Costs of HIV medical care in the era of highly active antiretroviral therapy*. AIDS 13(8): 963-9.

Gebrekristos, H. T., Mlisana, K. P. and Karim, Q. A. (2005). *Patients' readiness to start highly active antiretroviral treatment for HIV*. British Medical Journal 331(7519): 772-5.

Gellaitry, G., Cooper, V., Davis, C., Fisher, M., Date, H. L. and Horne, R. (2005). *Patients' perception of information about HAART: impact on treatment decisions*. AIDS Care 17(3): 367-76.

Getahun, A., Tansuphasawadikul, S., Desakorn, V., Dhitavat, J. and Pitisuttithum, P. (2006). *Efficacy and safety of generic fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-vir) in advanced HIV infection*. Journal of the Medical Association of Thailand 89(9): 1472-8.

Ghani, A. C., Donnelly, C. A. and Anderson, R. M. (2003). *Patterns of antiretroviral use in the United States of America: analysis of three observational databases*. HIV Medicine 4(1): 24-32.

Gilks, C. F. (2001). *HIV care in non-industrialised countries*. British Medical Bulletin 58: 171-86.

Gill, C. J., Griffith, J. L., Jacobson, D., Skinner, S., Gorbach, S. L. and Wilson, I. B. (2002). *Relationship of HIV viral loads, CD4 counts, and HAART use to health-related quality of life*. Journal of Acquired Immune Deficiency Syndrome 30(5): 485-92.

Global_Fund (2005). The Global Fund to Fight AIDS, Tuberculosis and Malaria Web page, Available at http://www.theglobalfund.org/en. Accessed June 1, 2005.

Gortmaker, S. L., Hughes, M., Cervia, J., Brady, M., Johnson, G. M., Seage, G. R., 3rd, Song, L. Y., Dankner, W. M. and Oleske, J. M. (2001). *Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1*. New England Journal of Medicine 345(21): 1522-8.

Griffiths, P. D., Edwards, M. H., Forbes, A., Harris, R. L. and Ritchie, G. (2007). *Effectiveness of intermediate care in nursing-led in-patient units*. Cochrane Database Syst Rev(2): CD002214.

Gross, R., Bilker, W. B., Friedman, H. M., Coyne, J. C. and Strom, B. L. (2002). *Provider inaccuracy in assessing adherence and outcomes with newly initiated antiretroviral therapy*. AIDS 16(13): 1835-7.

Guaraldi, G., Murri, R., Orlando, G., Giovanardi, C., Squillace, N., Vandelli, M., Beghetto, B., Nardini, G., De Paola, M., Esposito, R. and Wu, A. W. (2008). *Severity of lipodystrophy is associated with decreased health-related quality of life*. AIDS Patient Care & STDS 22(7): 577-85.

Haddad, M., Inch, C., Glazier, R. H., Wilkins, A. L., Urbshott, G., Bayoumi, A. and Rourke, S. (2000). *Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS*. Cochrane Database Syst Rev(3): CD001442.

Health, M. o. P. (1998). Report of HIV sero-sentinel surveillance from 1989-1997, Epidemiology Division, Ministry of Public Health, Nonthaburi, Thailand.

Health, M. o. P. (2006). Monthly epidemiological surveillance report. Bangkok, Division of Epidemiology. Ministry of Public Health, The Royal Thai Government.

Hengel, R. L., Allende, M. C., Dewar, R. L., Metcalf, J. A., Mican, J. M. and Lane, H. C. (2002). *Increasing CD4+ T cells specific for tuberculosis correlate with improved clinical immunity after highly active antiretroviral therapy*. AIDS Research & Human Retroviruses 18(13): 969-75.

Henry, K. (2000). *The case for more cautious, patient-focused antiretroviral therapy*. Annals of Internal Medicine 132(4): 306-11.

Herlitz, C. A. and Steel, J. L. (2001). *Highly active antiretroviral therapy (HAART). Awareness and beliefs about infectivity and the influence on sexual behaviour in the general population of Sweden*. European Journal of Public Health 11(3): 251-6.

Hermankova, M., Ray, S. C., Ruff, C., Powell-Davis, M., Ingersoll, R., D'Aquila, R. T., Quinn, T. C., Siliciano, J. D., Siliciano, R. F. and Persaud, D. (2001). *HIV-1 drug resistance profiles in children and adults with viral load of <50 copies/ml receiving combination therapy*. Journal of the American Medical Association 286(2): 196-207.

Hill, A. M., DeMasi, R. and Dawson, D. (1998). *Meta-analysis of antiretroviral effects on HIV-1 RNA, CD4 cell count and progression to AIDS or death*. Antiviral Therapy 3(3): 139-45.

Himelhoch, S., Moore, R. D., Treisman, G. and Gebo, K. A. (2004). *Does the presence of a current psychiatric disorder in AIDS patients affect the initiation of antiretroviral treatment and duration of therapy?* Journal of Acquired Immune Deficiency Syndrome 37(4): 1457-63.

Hiransuthikul, N., Hiransuthikul, P. and Kanasook, Y. (2007). *Lipid profiles of Thai adult HIV-infected patients receiving protease inhibitors*. Southest Asian Journal of Tropical Medicine and Public Health 38(1): 69-77.

Hirsch, M. S., Brun-Vezinet, F., Clotet, B., Conway, B., Kuritzkes, D. R., D'Aquila, R. T., Demeter, L. M., Hammer, S. M., Johnson, V. A., Loveday, C., Mellors, J. W., Jacobsen, D. M. and Richman, D. D. (2003). *Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel*. Clinical Infectious Diseases 37(1): 113-28.

Hirsch, M. S., Brun-Vezinet, F., D'Aquila, R. T., Hammer, S. M., Johnson, V. A., Kuritzkes, D. R., Loveday, C., Mellors, J. W., Clotet, B., Conway, B., Demeter, L. M., Vella, S., Jacobsen, D. M. and Richman, D. D. (2000). *Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel*. Journal of the American Medical Association 283(18): 2417-26.

Hirsch, M. S., Conway, B., D'Aquila, R. T., Johnson, V. A., Brun-Vezinet, F., Clotet, B., Demeter, L. M., Hammer, S. M., Jacobsen, D. M., Kuritzkes, D. R., Loveday, C., Mellors, J. W., Vella, S. and Richman, D. D. (1998). *Antiretroviral drug resistance testing in adults with HIV infection: implications for clinical management. International AIDS Society--USA Panel*. Journal of the American Medical Association 279(24): 1984-91.

Hogg, R. S., Strathdee, S. A., Craib, K. J., O'Shaughnessy, M. V., Montaner, J. S. and Schechter, M. T. (1994). *Lower socioeconomic status and shorter survival following HIV infection*. Lancet 344(8930): 1120-4.

Hogg, R. S., Weber, A. E., Craib, K. J., Anis, A. H., O'Shaughnessy, M. V., Schechter, M. T. and Montaner, J. S. (1998). *One world, one hope: the cost of providing antiretroviral therapy to all nations*. AIDS 12(16): 2203-9.

Horrocks, S., Anderson, E. and Salisbury, C. (2002). *Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors*. British Medical Journal 324(7341): 819-23.

Huebner, D. M., Rebchook, G. M. and Kegeles, S. M. (2004). *A longitudinal study of the association between treatment optimism and sexual risk behavior in young adult gay and bisexual men*. Journal of Acquired Immune Deficiency Syndrome 37(4): 1514-9.

Hughes, M. D., Johnson, V. A., Hirsch, M. S., Bremer, J. W., Elbeik, T., Erice, A., Kuritzkes, D. R., Scott, W. A., Spector, S. A., Basgoz, N., Fischl, M. A. and D'Aquila, R. T. (1997). *Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team.* Annals of Internal Medicine 126(12): 929-38.

Hulgan, T., Raffanti, S., Kheshti, A., Blackwell, R. B., Rebeiro, P. F., Barkanic, G., Ritz, B. and Sterling, T. R. (2005). *CD4 lymphocyte percentage predicts disease progression in HIV-infected patients initiating highly active antiretroviral therapy with CD4 lymphocyte counts >350 lymphocytes/mm3.* Journal of Infectious Diseases 192(6): 950-7.

Hunt, P. W., Deeks, S. G., Rodriguez, B., Valdez, H., Shade, S. B., Abrams, D. I., Kitahata, M. M., Krone, M., Neilands, T. B., Brand, R. J., Lederman, M. M. and Martin, J. N. (2003). *Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy.* AIDS 17(13): 1907-15.

Ichikawa, M. and Natpratan, C. (2004). *Quality of life among people living with HIV/AIDS in northern Thailand: MOS-HIV Health Survey.* Quality of Life Research 13(3): 601-10.

Ickovics, J. R., Forsyth, B., Ethier, K. A., Harris, P. and Rodin, J. (1996). *Delayed entry into health care for women with HIV disease.* AIDS Patient Care and STDS 10(1): 21-4.

Institute, A. M. S. R. (1998). Report on HIV prevalence rate on newly military conscript, Royal Thai Army 1990-1997, Army Medical Science Research Institute, Royal Thai Army, Bangkok.

Ivers, L. C., Kendrick, D. and Doucette, K. (2005). *Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature*. Clinical Infectious Diseases 41(2): 217-24.

Jacobson, L. P., Li, R., Phair, J., Margolick, J. B., Rinaldo, C. R., Detels, R. and Munoz, A. (2002). *Evaluation of the effectiveness of highly active antiretroviral therapy in persons with human immunodeficiency virus using biomarker-based equivalence of disease progression*. American Journal of Epidemiology 155(8): 760-70.

Jaffar, S., Govender, T., Garrib, A., Welz, T., Grosskurth, H., Smith, P. G., Whittle, H. and Bennish, M. L. (2005). *Antiretroviral treatment in resource-poor settings: public health research priorities*. Tropical Medicine and International Health 10(4): 295-9.

Jelsma, J., Maclean, E., Hughes, J., Tinise, X. and Darder, M. (2005). *An investigation into the health-related quality of life of individuals living with HIV who are receiving HAART*. AIDS Care 17(5): 579-88.

Jia, H., Uphold, C., Wu, S., Chen, G. and Duncan, P. (2005). *Predictors of changes in health-related quality of life among men with HIV infection in the HAART era*. AIDS Patient Care and STDS 19(6): 395-405.

Jia, H., Uphold, C. R., Zheng, Y., Wu, S., Chen, G. J., Findley, K. and Duncan, P. W. (2007). *A further investigation of health-related quality of life over time among men with HIV infection in the HAART era*. Quality of Life Research 16(6): 961-8.

Jones, R. and Gazzard, B. (2006). *The cost of antiretroviral drugs and influence on prescribing policies*. International Journal of STDs & AIDS 17(8): 499-506.

Kahn, J. G., Haile, B., Kates, J. and Chang, S. (2001). *Health and federal budgetary effects of increasing access to antiretroviral medications for HIV by expanding Medicaid.* American Journal of Public Health 91(9): 1464-73.

Kahn, J. G., Zhang, X., Cross, L. T., Palacio, H., Birkhead, G. S. and Morin, S. F. (2002). *Access to and use of HIV antiretroviral therapy: variation by race/ethnicity in two public insurance programs in the U.S.* Public Health Rep 117(3): 252-62; discussion 231-2.

Kanshana, S. and Simonds, R. J. (2002). *National program for preventing mother-child HIV transmission in Thailand: successful implementation and lessons learned.* AIDS 16(7): 953-9.

Kaplan, J. E., Hanson, D. L., Cohn, D. L., Karon, J., Buskin, S., Thompson, M., Fleming, P. and Dworkin, M. S. (2003). *When to begin highly active antiretroviral therapy? Evidence supporting initiation of therapy at CD4+ lymphocyte counts <350 cells/microL.* Clinical Infectious Diseases 37(7): 951-8.

Kapp, C. (2003). *Sparks fly over patents and vital drugs at world health assembly.* Lancet 361(9372): 1873.

Katabira, E. T. and Oelrichs, R. B. (2007). *Scaling up antiretroviral treatment in resource-limited settings: successes and challenges.* AIDS 21 Suppl 4: S5-10.

Kawado, M., Hashimoto, S., Yamaguchi, T., Oka, S., Yoshizaki, K., Kimura, S., Fukutake, K., Higasa, S. and Shirasaka, T. (2006). *Difference of progression to AIDS according to CD4 cell count, plasma HIV RNA level and the use of antiretroviral therapy among HIV patients infected through blood products in japan.* Journal of Epidemiology 16(3): 101-6.

Keiser, P., Nassar, N., Kvanli, M. B., Turner, D., Smith, J. W. and Skiest, D. (2001). *Long-term impact of highly active antiretroviral therapy on HIV-related health care costs*. Journal of Acquired Immune Deficiency Syndrome 27(1): 14-9.

Kerr, S. J., Duncombe, C., Avihingsanon, A., Ananworanich, J., Boyd, M., Sopa, B., Medtech, B., Chuenyam, T., Cooper, D. A., Lange, J. M., Phanuphak, P. and Ruxrungtham, K. (2007). *Dyslipidemia in an Asian population after treatment for two years with protease inhibitor-containing regimens*. J Int Assoc Physicians AIDS Care (Chic Ill) 6(1): 36-46.

Keruly, J. C., Conviser, R. and Moore, R. D. (2002). *Association of medical insurance and other factors with receipt of antiretroviral therapy*. American Journal of Public Health 92(5): 852-7.

Kitahata, M. M., Koepsell, T. D., Deyo, R. A., Maxwell, C. L., Dodge, W. T. and Wagner, E. H. (1996). *Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival*. New England Journal of Medicine 334(11): 701-6.

Kitajima, T., Kobayashi, Y., Chaipah, W., Sato, H., Chadbunchachai, W. and Thuennadee, R. (2003). *Costs of medical services for patients with HIV/AIDS in Khon Kaen, Thailand*. AIDS 17(16): 2375-81.

Kitajima, T., Kobayashi, Y., Chaipah, W., Sato, H., Toyokawa, S., Chadbunchachai, W. and Thuennadee, R. (2005). *Access to antiretroviral therapy among HIV/AIDS patients in Khon Kaen Province, Thailand*. AIDS Care 17(3): 359-66.

Kleeberger, C. A., Buechner, J., Palella, F., Detels, R., Riddler, S., Godfrey, R. and Jacobson, L. P. (2004). *Changes in adherence to highly active antiretroviral*

therapy medications in the Multicenter AIDS Cohort Study. AIDS 18(4): 683-8.

Kober, K. and Van Damme, W. (2004). *Scaling up access to antiretroviral treatment in southern Africa: who will do the job?* Lancet 364(9428): 103-7.

Koblin, B. A., Perdue, T., Ren, L., Thiede, H., Guilin, V., MacKellar, D. A., Valleroy, L. A. and Torian, L. V. (2003). *Attitudes about combination HIV therapies: the next generation of gay men at risk*. Journal of Urban Health 80(3): 510-9.

Kovsted, J. (2005). *Scaling up AIDS treatment in developing countries: A review of current and future arguments*. Development Policy Review 23(4): 465-482.

Krebs, D. W., Chi, B. H., Mulenga, Y., Morris, M., Cantrell, R. A., Mulenga, L., Levy, J., Sinkala, M. and Stringer, J. S. (2008). *Community-based follow-up for late patients enrolled in a district-wide programme for antiretroviral therapy in Lusaka, Zambia*. AIDS Care 20(3): 311-7.

Krentz, H. B., Auld, M. C. and Gill, M. J. (2003). *The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001*. Canadian Medical Association Journal 169(2): 106-10.

Kumar, A., Kilaru, K. R., Forde, S. and Roach, T. C. (2006). *Changing HIV infection-related mortality rate and causes of death among persons with HIV infection before and after the introduction of highly active antiretroviral therapy: analysis of all HIV-related deaths in Barbados, 1997-2005*. J Int Assoc Physicians AIDS Care (Chic Ill) 5(3): 109-14.

Kumarasamy, N., Solomon, S., Flanigan, T. P., Hemalatha, R., Thyagarajan, S. P. and Mayer, K. H. (2003). *Natural history of human immunodeficiency virus disease in southern India*. Clinical Infectious Diseases 36(1): 79-85.

Lallemant, M., Jourdain, G., Le Coeur, S., Kim, S., Koetsawang, S., Comeau, A. M., Phoolcharoen, W., Essex, M., McIntosh, K. and Vithayasai, V. (2000). *A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators*. New England Journal of Medicine 343(14): 982-91.

Landman, R., Moatti, J. P., Perrin, V. and Huard, P. (2000). *Variability of attitudes toward early initiation of HAART for HIV infection: a study of French prescribing physicians*. AIDS Care 12(6): 711-6.

Landon, B. E., Wilson, I. B., Cohn, S. E., Fichtenbaum, C. J., Wong, M. D., Wenger, N. S., Bozzette, S. A., Shapiro, M. F. and Cleary, P. D. (2003). *Physician specialization and antiretroviral therapy for HIV*. Journal of General Internal Medicine 18(4): 233-41.

Lange, J. M. and van der Waals, F. W. (2002). *Prioritising access to antiretroviral therapy in resource-poor settings*. Journal of HIV Therapy 7(3): 59-62.

Lapphra, K., Vanprapar, N., Phongsamart, W., Chearskul, P. and Chokephaibulkit, K. (2005). *Dyslipidemia and lipodystrophy in HIV-infected Thai children on highly active antiretroviral therapy (HAART)*. Journal of the Medical Association of Thailand 88(7): 956-66.

Lau, B., Gange, S. J. and Moore, R. D. (2007). *Risk of non-AIDS-related mortality may exceed risk of AIDS-related mortality among individuals enrolling into care with CD4+ counts greater than 200 cells/mm3*. Journal of Acquired Immune Deficiency Syndrome 44(2): 179-87.

Laurant, M., Reeves, D., Hermens, R., Braspenning, J., Grol, R. and Sibbald, B. *Substitution of doctors by nurses in primary care. The Cochrane Database of Systematic Reviews 2004, Issue 4.*

Laurent, C., Diakhate, N., Gueye, N. F., Toure, M. A., Sow, P. S., Faye, M. A., Gueye, M., Laniece, I., Toure Kane, C., Liegeois, F., Vergne, L., Mboup, S., Badiane, S., Ndoye, I. and Delaporte, E. (2002). *The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study*. AIDS 16(10): 1363-70.

Lenderking, W. R., Gelber, R. D., Cotton, D. J., Cole, B. F., Goldhirsch, A., Volberding, P. A. and Testa, M. A. (1994). *Evaluation of the quality of life associated with zidovudine treatment in asymptomatic human immunodeficiency virus infection. The AIDS Clinical Trials Group*. New England Journal of Medicine 330(11): 738-43.

Lert, F. and Kazatchkine, M. D. (2007). *Antiretroviral HIV treatment and care for injecting drug users: an evidence-based overview*. International Journal of Drug Policy 18(4): 255-61.

Levi, G. C. and Vitoria, M. A. (2002). *Fighting against AIDS: the Brazilian experience*. AIDS 16(18): 2373-83.

Levy, A. R., James, D., Johnston, K. M., Hogg, R. S., Harrigan, P. R., Harrigan, B. P., Sobolev, B. and Montaner, J. S. (2006). *The direct costs of HIV/AIDS care*. Lancet Infectious Diseases 6(3): 171-7.

Liu, C., Johnson, L., Ostrow, D., Silvestre, A., Visscher, B. and Jacobson, L. P. (2006). *Predictors for lower quality of life in the HAART era among HIV-infected men*. Journal of Acquired Immune Deficiency Syndrome 42(4): 470-7.

Liu, C., Ostrow, D., Detels, R., Hu, Z., Johnson, L., Kingsley, L. and Jacobson, L. P. (2006). *Impacts of HIV infection and HAART use on quality of life*. Quality of Life Research 15(6): 941-9.

Lloyd-Smith, E., Brodkin, E., Wood, E., Kerr, T., Tyndall, M. W., Montaner, J. S. and Hogg, R. S. (2006). *Impact of HAART and injection drug use on life expectancy of two HIV-positive cohorts in British Columbia*. AIDS 20(3): 445-50.

Loewenson, R. and McCoy, D. (2004). *Access to antiretroviral treatment in Africa*. British Medical Journal 328(7434): 241-2.

Loughlin, A., Metsch, L., Gardner, L., Anderson-Mahoney, P., Barrigan, M. and Strathdee, S. (2004). *Provider barriers to prescribing HAART to medically-eligible HIV-infected drug users*. AIDS Care 16(4): 485-500.

Louie, J. K., Hsu, L. C., Osmond, D. H., Katz, M. H. and Schwarcz, S. K. (2002). *Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994-1998*. Journal of Infectious Diseases 186(7): 1023-7.

Louwagie, G. M., Bachmann, M. O., Meyer, K., Booysen Fle, R., Fairall, L. R. and Heunis, C. (2007). *Highly active antiretroviral treatment and health related quality of life in South African adults with human immunodeficiency virus infection: A cross-sectional analytical study*. BMC Public Health 7: 244.

Lucas, G. M. (2005). *Antiretroviral adherence, drug resistance, viral fitness and HIV disease progression: a tangled web is woven*. Journal of Antimicrobial Chemotherapy 55(4): 413-6.

Lynen, L., Thai, S., De Munter, P., Leang, B., Sokkab, A., Schrooten, W., Huyst, V., Kestens, L., Jacques, G., Colebunders, R., Menten, J. and van den Ende, J.

(2006). *The added value of a CD4 count to identify patients eligible for highly active antiretroviral therapy among HIV-positive adults in Cambodia.* Journal of Acquired Immune Deficiency Syndrome 42(3): 322-4.

Lyttleton, C. (1996). *Messages of distinction: the HIV/AIDS media campaign in Thailand.* Medical Anthropology 16(4): 363-89.

Lyttleton, C., Beesey, A. and Sitthikriengkrai, M. (2007). *Expanding community through ARV provision in Thailand.* AIDS Care 19 Suppl 1: S44-53.

Makombe, S., Libamba, E., Mhango, E., de Ascurra Teck, O., Aberle-Grasse, J., Hochgesang, M., Schouten, E. J. and Harries, A. D. (2006). *Who is accessing antiretroviral therapy during national scale-up in Malawi?* Transactions of the Royal Society of Tropical Medicine & Hygiene 100(10): 975-9.

Maneesriwongul, W. L., Tulathong, S., Fennie, K. P. and Williams, A. B. (2006). *Adherence to antiretroviral medication among HIV-positive patients in Thailand.* Journal of Acquired Immune Deficiency Syndrome 43 Suppl 1: S119-22.

Mannheimer, S. B., Matts, J., Telzak, E., Chesney, M., Child, C., Wu, A. W. and Friedland, G. (2005). *Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence.* AIDS Care 17(1): 10-22.

Manosuthi, W., Chaovavanich, A., Tansuphaswadikul, S., Prasithsirikul, W., Inthong, Y., Chottanapund, S., Sittibusaya, C., Moolasart, V., Termvises, P. and Sungkanuparph, S. (2007). *Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV-infected patients in a resource-limited setting.* Journal of Infection 55(5): 464-9.

Marelich, W. D., Johnston Roberts, K., Murphy, D. A. and Callari, T. (2002). *HIV/AIDS patient involvement in antiretroviral treatment decisions*. AIDS Care 14(1): 17-26.

Marmot, M. G., Smith, G. D., Stansfeld, S., Patel, C., North, F., Head, J., White, I., Brunner, E. and Feeney, A. (1991). *Health inequalities among British civil servants: the Whitehall II study*. Lancet 337(8754): 1387-93.

Marseille, E., Hofmann, P. B. and Kahn, J. G. (2002). *HIV prevention before HAART in sub-Saharan Africa*. Lancet 359(9320): 1851-6.

Mayor, A. M., Gomez, M. A., Fernandez, D. M., Rios-Olivares, E., Thomas, J. C. and Hunter, R. F. (2006). *Morbidity and mortality profile of human immunodeficiency virus-infected patients with and without hepatitis C co-infection*. American Journal of Tropical Medicine & Hygiene 74(2): 239-45.

Mayor, A. M., Gomez, M. A., Rios-Oliveras, E. and Hunter-Mellado, R. F. (2005). *Mortality trends of HIV-infected patients after the introduction of highly active antiretroviral therapy: analysis of a cohort of 3,322 HIV-infected persons*. Ethnicity & Disease 15(4 Suppl 5): S5-57-62.

McCance-Katz, E. F. (2005). *Treatment of opioid dependence and coinfection with HIV and hepatitis C virus in opioid-dependent patients: the importance of drug interactions between opioids and antiretroviral agents*. Clinical Infectious Diseases 41 Suppl 1: S89-95.

McDonald, K., Bartos, M. and Rosenthal, D. (2001). *Australian women living with HIV/AIDS are more sceptical than men about antiretroviral treatment*. AIDS Care 13(1): 15-26.

McFarland, W., Chen, S., Hsu, L., Schwarcz, S. and Katz, M. (2003). *Low socioeconomic status is associated with a higher rate of death in the era of*

highly active antiretroviral therapy, San Francisco. Journal of Acquired Immune Deficiency Syndrome 33(1): 96-103.

McKinney, M. M. and Marconi, K. M. (2002). *Delivering HIV services to vulnerable populations: a review of CARE Act-funded research*. Public Health Report 117(2): 99-113.

McNaghten, A. D., Hanson, D. L., Dworkin, M. S. and Jones, J. L. (2003). *Differences in prescription of antiretroviral therapy in a large cohort of HIV-infected patients*. Journal of Acquired Immune Deficiency Syndrome 32(5): 499-505.

Mellors, J. W., Munoz, A., Giorgi, J. V., Margolick, J. B., Tassoni, C. J., Gupta, P., Kingsley, L. A., Todd, J. A., Saah, A. J., Detels, R., Phair, J. P. and Rinaldo, C. R., Jr. (1997). *Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection*. Annals of Internal Medicine 126(12): 946-54.

Melo, A. C., Caiaffa, W. T., Cesar, C. C., Dantas, R. V. and Couttolenc, B. F. (2006). *Utilization of HIV/AIDS treatment services: comparing injecting drug users and other clients*. Cadernos de Saude Publica 22(4): 803-13.

Meng, X., Anderson, A. F., Hou, X., Wang, Y., Sun, L., Zhang, X., Li, Z., Qui, B., Lang, Y. and Zhang, L. (2006). *A pilot project for the effective delivery of HAART in rural China*. AIDS Patient Care & STDS 20(3): 213-9.

Merito, M., Bonaccorsi, A., Pammolli, F., Riccaboni, M., Baio, G., Arici, C., Monforte, A. D., Pezzotti, P., Corsini, D., Tramarin, A., Cauda, R., Colangeli, V. and Pastore, G. (2005). *Economic evaluation of HIV treatments: the I.CO.N.A. cohort study*. Health Policy 74(3): 304-13.

Michael, C. G., Kirk, O., Mathiesen, L. and Nielsen, S. D. (2002). *The naive CD4+ count in HIV-1-infected patients at time of initiation of highly active*

antiretroviral therapy is strongly associated with the level of immunological recovery. Scandinavian Journal of Infectious Diseases 34(1): 45-9.

Miles, K., Penny, N., Power, R. and Mercey, D. (2003). *Comparing doctor- and nurse-led care in a sexual health clinic: patient satisfaction questionnaire*. Journal of Advanced Nursing 42(1): 64-72.

Miller, L. G. and Hays, R. D. (2000). *Measuring adherence to antiretroviral medications in clinical trials*. HIV Clin Trials 1(1): 36-46.

Mills, E. J., Nachega, J. B., Bangsberg, D. R., Singh, S., Rachlis, B., Wu, P., Wilson, K., Buchan, I., Gill, C. J. and Cooper, C. (2006). *Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators*. PLoS Medicine 3(11): e438.

Miners, A. H., Sabin, C. A., Mocroft, A., Youle, M., Fisher, M. and Johnson, M. (2001). *Health-related quality of life in individuals infected with HIV in the era of HAART*. HIV Clinical Trials 2(6): 484-92.

Moatti, J. P., N'Doye, I., Hammer, S. M., Hale, P. and Kazatchkine, M. (2003). *Antiretroviral treatment for HIV infection in developing countries: an attainable new paradigm*. National Medicine 9(12): 1449-52.

Moatti, J. P., Spire, B. and Kazatchkine, M. (2004). *Drug resistance and adherence to HIV/AIDS antiretroviral treatment: against a double standard between the north and the south*. AIDS 18 Suppl 3: S55-61.

Moayyeri, A. and Soltani, A. (2005). *Evidence based medicine: does it make a difference? ...as may be a top down approach*. British Medical Journal 330(7482): 93-4; discussion 94.

Mocroft, A., Gatell, J., Reiss, P., Ledergerber, B., Kirk, O., Vella, S., Blaxhult, A., Phillips, A. N. and Lundgren, J. (2004). *Causes of death in HIV infection:*

the key determinant to define the clinical response to anti-HIV therapy. AIDS 18(17): 2333-7.

Monnerat, B. Z., Cerutti Junior, C., Canicali, S. C. and Motta, T. R. (2008). *Clinical and biochemical evaluation of HIV-related lipodystrophy in an ambulatory population from the Hospital Universitario Cassiano Antonio de Morais, Vitoria, ES, Brazil*. Brazilian Journal of Infectious Diseases 12(4): 364-8.

Montessori, V., Press, N., Harris, M., Akagi, L. and Montaner, J. S. (2004). *Adverse effects of antiretroviral therapy for HIV infection*. Cmaj 170(2): 229-38.

Moore, R. D. (2000). *Cost effectiveness of combination HIV therapy: 3 years later*. Pharmacoeconomics 17(4): 325-30.

Moore, R. D., Stanton, D., Gopalan, R. and Chaisson, R. E. (1994). *Racial differences in the use of drug therapy for HIV disease in an urban community*. New England Journal of Medicine 330(11): 763-8.

MOPH (2004). The National Access to Antiretroviral Programs for People who living with HIV/AIDS. Nonthaburi, Thailand, AIDS Division, Communicable Disease Control Department, Ministry of Public Health.

MOPH (2005). AIDS cases report: Catagorized by Province and Region Department of Disease Control, M. o. P. H., Thailand.

Morin, S. F., Sengupta, S., Cozen, M., Richards, T. A., Shriver, M. D., Palacio, H. and Kahn, J. G. (2002). *Responding to racial and ethnic disparities in use of HIV drugs: analysis of state policies*. Public Health Report 117(3): 263-72; discussion 231-2.

Morrison, M. F., Petitto, J. M., Ten Have, T., Gettes, D. R., Chiappini, M. S., Weber, A. L., Brinker-Spence, P., Bauer, R. M., Douglas, S. D. and Evans,

D. L. (2002). *Depressive and anxiety disorders in women with HIV infection.* American Journal of Psychiatry 159(5): 789-96.

Murray, C. and Frenk, J. (2001). *World Health Report 2000: a step towards evidence-based health policy.* Lancet 357(9269): 1698-700.

Muula, A. S., Chipeta, J., Siziya, S., Rudatsikira, E., Mataya, R. H. and Kataika, E. (2007). *Human resources requirements for highly active antiretroviral therapy scale-up in Malawi.* BMC Health Services Research 7: 208.

Nagelkerke, N. J., Jha, P., de Vlas, S. J., Korenromp, E. L., Moses, S., Blanchard, J. F. and Plummer, F. A. (2002). *Modelling HIV/AIDS epidemics in Botswana and India: impact of interventions to prevent transmission.* Bulletin of the World Health Organisation 80(2): 89-96.

Nakimuli-Mpungu, E., Musisi, S., Mpungu, S. K. and Katabira, E. (2006). *Primary mania versus HIV-related secondary mania in Uganda.* American Journal of Psychiatry 163(8): 1349-54; quiz 1480.

Natu, S. A. and Daga, S. R. (2007). *Antiretroviral therapy in children: Indian experience.* Indian Pediatrics 44(5): 339-43.

NESDB (2004). Thailand NESDB; Thailand's Official Poverty Lines. . Bangkok, National Economic and Social Development Board of Thailand**:** 1-14.

Nieuwkerk, P. T., Gisolf, E. H., Colebunders, R., Wu, A. W., Danner, S. A. and Sprangers, M. A. (2000). *Quality of life in asymptomatic- and symptomatic HIV infected patients in a trial of ritonavir/saquinavir therapy. The Prometheus Study Group.* AIDS 14(2): 181-7.

Nieuwkerk, P. T., Gisolf, E. H., Reijers, M. H., Lange, J. M., Danner, S. A. and Sprangers, M. A. (2001). *Long-term quality of life outcomes in three*

antiretroviral treatment strategies for HIV-1 infection. AIDS 15(15): 1985-91.

Nieuwkerk, P. T., Gisolf, E. H., Reijers, M. H., Lange, J. M., Danner, S. A. and Sprangers, M. A. (2001). *Long-term quality of life outcomes in three antiretroviral treatment strategies for HIV-1 infection*. AIDS 15(15): 1985-91.

Nieuwkerk, P. T. and Oort, F. J. (2005). *Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis*. Journal of Acquired Immune Deficiency Syndrome 38(4): 445-8.

Nikolic-Djokic, D., Essajee, S., Rigaud, M., Kaul, A., Chandwani, S., Hoover, W., Lawrence, R., Pollack, H., Sitnitskaya, Y., Hagmann, S., Jean-Philippe, P., Chen, S. H., Radding, J., Krasinski, K. and Borkowsky, W. (2002). *Immunoreconstitution in children receiving highly active antiretroviral therapy depends on the CD4 cell percentage at baseline*. Journal of Infectious Diseases 185(3): 290-8.

Nuesch, R., Geigy, N., Schaedler, E. and Battegay, M. (2002). *Effect of highly active antiretroviral therapy on hospitalization characteristics of HIV-infected patients*. European Journal of Clinical Microbiology in Infectious Diseases 21(9): 684-7.

Nuesch, R., Srasuebkul, P., Ananworanich, J., Ruxrungtham, K., Phanuphak, P. and Duncombe, C. (2006). *Monitoring the toxicity of antiretroviral therapy in resource limited settings: a prospective clinical trial cohort in Thailand.* Journal of Antimicrobial Chemotherapy 58(3): 637-44.

Nunn, A. S., Fonseca, E. M., Bastos, F. I., Gruskin, S. and Salomon, J. A. (2007). *Evolution of antiretroviral drug costs in Brazil in the context of free and universal access to AIDS treatment*. PLoS Medicine 4(11): e305.

O'Brien, W. A., Hartigan, P. M., Daar, E. S., Simberkoff, M. S. and Hamilton, J. D. (1997). *Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. VA Cooperative Study Group on AIDS*. Ann Intern Med 126(12): 939-45.

Obermeyer, C. M. and Rajkumar, R. (2004). *HAART and sexual risk behavior*. Journal of the American Medical Association 292(19): 2335; author reply 2336.

Offredy, M. and Townsend, J. (2000). *Nurse practitioners in primary care*. Family Practice 17(6): 564-9.

Optimism, I. C. o. H. (2003). *HIV treatments optimism among gay men: an international perspective*. Journal of Acquired Immune Deficiency Syndrome 32(5): 545-50.

Orrell, C. (2005). *Antiretroviral adherence in a resource-poor setting*. Current HIV/AIDS Report 2(4): 171-6.

Orrell, C., Bangsberg, D. R., Badri, M. and Wood, R. (2003). *Adherence is not a barrier to successful antiretroviral therapy in South Africa*. AIDS 17(9): 1369-75.

Over, M., Revenga, A., Masaki, E., Peerapatanapokin, W., Gold, J., Tangcharoensathien, V. and Thanprasertsuk, S. (2007). *The economics of effective AIDS treatment in Thailand*. AIDS 21 Suppl 4: S105-16.

Pacheco, A. G., Tuboi, S. H., Faulhaber, J. C., Harrison, L. H. and Schechter, M. (2008). *Increase in non-AIDS related conditions as causes of death among*

HIV-infected individuals in the HAART era in Brazil. PLoS ONE 3(1): e1531.

Page, J., Heller, R. F., Kinlay, S., Lim, L. L., Qian, W., Suping, Z., Kongpatanakul, S., Akhtar, M., Khedr, S. and Macharia, W. (2003). *Attitudes of developing world physicians to where medical research is performed and reported.* BMC Public Health 3: 6.

Palacio, H., Kahn, J. G., Richards, T. A. and Morin, S. F. (2002). *Effect of race and/or ethnicity in use of antiretrovirals and prophylaxis for opportunistic infection: a review of the literature*. Public Health Report 117(3): 233-51; discussion 231-2.

Palella, F. J., Jr., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., Aschman, D. J. and Holmberg, S. D. (1998). *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators*. New England Journal of Medicine 338(13): 853-60.

Palella, F. J., Jr., Deloria-Knoll, M., Chmiel, J. S., Moorman, A. C., Wood, K. C., Greenberg, A. E. and Holmberg, S. D. (2003). *Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata.* Annals of Internal Medicine 138(8): 620-6.

Panpanich, R. (2004). A Rapid Situation Analysis of the Access to Care Project in Northern Thailand; "Horizons Final Report", Population Council.

Park-Wyllie, L. Y., Strike, C. S., Antoniou, T. and Bayoumi, A. M. (2007). *Adverse quality of life consequences of antiretroviral medications*. AIDS Care 19(2): 252-7.

Parsons, T. D., Braaten, A. J., Hall, C. D. and Robertson, K. R. (2006). *Better quality of life with neuropsychological improvement on HAART*. Health and Quality of Life Outcomes 4: 11.

Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., Wagener, M. M. and Singh, N. (2000). *Adherence to protease inhibitor therapy and outcomes in patients with HIV infection*. Annals of Internal Medicine 133(1): 21-30.

PEPFAR (2006). The President's emergency plan for AIDS relief: report on work force capacity and HIV/AIDS

Phanuphak, P. (2004). *Antiretroviral treatment in resource-poor settings: what can we learn from the existing programmes in Thailand?* AIDS 18 Suppl 3: S33-8.

Philips, M., Zachariah, R. and Venis, S. (2008). *Task shifting for antiretroviral treatment delivery in sub-Saharan Africa: not a panacea*. Lancet 371(9613): 682-4.

Phillips, A. N., Gazzard, B. G., Clumeck, N., Losso, M. H. and Lundgren, J. D. (2007). *When should antiretroviral therapy for HIV be started?* British Medical Journal 334(7584): 76-8.

Phoolcharoen, W. (1998). *HIV/AIDS prevention in Thailand: success and challenges*. Science 280(5371): 1873-4.

Pilcher, C. D., Miller, W. C., Beatty, Z. A. and Eron, J. J. (1999). *Detectable HIV-1 RNA at levels below quantifiable limits by amplicor HIV-1 monitor is associated with virologic relapse on antiretroviral therapy*. AIDS 13(11): 1337-42.

Ponnet, M., Frederix, K., Petdachai, W., Wilson, D., Eksaengsri, A. and Zachariah, R. (2005). *A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand.* International Journal of STDs & AIDS 16(6): 420-6.

Pontali, E. (2005). *Antiretroviral treatment in correctional facilities.* HIV Clinical Trials 6(1): 25-37.

Poundstone, K. E., Chaisson, R. E. and Moore, R. D. (2001). *Differences in HIV disease progression by injection drug use and by sex in the era of highly active antiretroviral therapy.* AIDS 15(9): 1115-23.

Poupard, M., Ngom Gueye, N. F., Thiam, D., Ndiaye, B., Girard, P. M., Delaporte, E., Sow, P. S. and Landman, R. (2007). *Quality of life and depression among HIV-infected patients receiving efavirenz- or protease inhibitor-based therapy in Senegal.* HIV Medicine 8(2): 92-5.

Preau, M., Leport, C., Salmon-Ceron, D., Carrieri, P., Portier, H., Chene, G., Spire, B., Choutet, P., Raffi, F. and Morin, M. (2004). *Health-related quality of life and patient-provider relationships in HIV-infected patients during the first three years after starting PI-containing antiretroviral treatment.* AIDS Care 16(5): 649-61.

Prescott N, K. C., Phoolcharoin W, Rojanapitayakorn W, Perriens J, Boonyuen D. . , (1996). *Formulating rational use of anti-retrovirals in Thailand.* XI International Conference on AIDS, Vancouver.

Protopopescu, C., Marcellin, F., Spire, B., Preau, M., Verdon, R., Peyramond, D., Raffi, F., Chene, G., Leport, C. and Carrieri, M. P. (2007). *Health-related quality of life in HIV-1-infected patients on HAART: a five-years*

longitudinal analysis accounting for dropout in the APROCO-COPILOTE cohort (ANRS CO-8). Quality of Life Research 16(4): 577-91.

Puthanakit, T., Aurpibul, L., Oberdorfer, P., Akarathum, N., Kanjananit, S., Wannarit, P., Sirisanthana, T. and Sirisanthana, V. (2007). *Hospitalization and mortality among HIV-infected children after receiving highly active antiretroviral therapy*. Clinical Infectious Diseases 44(4): 599-604.

Puthanakit, T., Aurpibul, L., Oberdorfer, P., Akarathum, N., Kanjanavanit, S., Wannarit, P., Sirisanthana, T. and Sirisanthana, V. (2007). *Sustained immunologic and virologic efficacy after four years of highly active antiretroviral therapy in human immunodeficiency virus infected children in Thailand*. Pediatric Infectious Diseases Journal 26(10): 953-6.

Puthanakit, T., Oberdorfer, A., Akarathum, N., Kanjanavanit, S., Wannarit, P., Sirisanthana, T. and Sirisanthana, V. (2005). *Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program*. Clinical Infectious Diseases 41(1): 100-7.

Rao, D., Kekwaletswe, T. C., Hosek, S., Martinez, J. and Rodriguez, F. (2007). *Stigma and social barriers to medication adherence with urban youth living with HIV*. AIDS Care 19(1): 28-33.

Rapiti, E., Porta, D., Forastiere, F., Fusco, D. and Perucci, C. A. (2000). *Socioeconomic status and survival of persons with AIDS before and after the introduction of highly active antiretroviral therapy. Lazio AIDS Surveillance Collaborative Group*. Epidemiology 11(5): 496-501.

Read, T., Mijch, A. and Fairley, C. K. (2003). *Adherence to antiretroviral therapy: are we doing enough?* International Medical Journal 33(5-6): 254-6.

Revicki, D. A., Moyle, G., Stellbrink, H. J. and Barker, C. (1999). *Quality of life outcomes of combination zalcitabine-zidovudine, saquinavir-zidovudine, and saquinavir-zalcitabine-zidovudine therapy for HIV-infected adults with CD4 cell counts between 50 and 350 per cubic millimeter. PISCES (SV14604) Study Group*. AIDS 13(7): 851-8.

Richman, D. D., Morton, S. C., Wrin, T., Hellmann, N., Berry, S., Shapiro, M. F. and Bozzette, S. A. (2004). *The prevalence of antiretroviral drug resistance in the United States*. AIDS 18(10): 1393-401.

Riedel, D. J., Gebo, K. A., Moore, R. D. and Lucas, G. M. (2008). *A ten-year analysis of the incidence and risk factors for acute pancreatitis requiring hospitalization in an urban HIV clinical cohort*. AIDS Patient Care & STDS 22(2): 113-21.

Rintamaki, L. S., Davis, T. C., Skripkauskas, S., Bennett, C. L. and Wolf, M. S. (2006). *Social stigma concerns and HIV medication adherence*. AIDS Patient Care & STDS 20(5): 359-68.

Rockstroh, J. K. and Spengler, U. (2004). *HIV and hepatitis C virus co-infection*. Lancet Infectious Diseases 4(7): 437-44.

Rockstroh, J. K. and Vogel, M. (2004). *Therapy of hepatitis C in HIV-coinfection*. European Journal of Medical Research 9(6): 304-8.

Rosen, S., Fox, M. P. and Gill, C. J. (2007). *Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review*. PLoS Medicine 4(10): e298.

Rutherford, G., Sangani, P. and Kennedy, G. *Three- or four- versus two-drug antiretroviral maintenance regimens for HIV infection. The Cochrane Database of Systematic Reviews 2003, Issue 4*.

Safrin, S., Finkelstein, D. M., Feinberg, J., Frame, P., Simpson, G., Wu, A., Cheung, T., Soeiro, R., Hojczyk, P. and Black, J. R. (1996). *Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group*. Annals of Internal Medicine 124(9): 792-802.

Salmon-Ceron, D., Mazeron, M. C., Chaput, S., Boukli, N., Senechal, B., Houhou, N., Katlama, C., Matheron, S., Fillet, A. M., Gozlan, J., Leport, C., Jeantils, V., Freymuth, F. and Costagliola, D. (2000). *Plasma cytomegalovirus DNA, pp65 antigenaemia and a low CD4 cell count remain risk factors for cytomegalovirus disease in patients receiving highly active antiretroviral therapy*. AIDS 14(8): 1041-9.

Sanchez, J. M., Ramos Amador, J. T., Fernandez de Miguel, S., Gonzalez Tomee, M. I., Rojo Conejo, P., Ferrnado Vivas, P., Clemente Vivas, J., Ruiz Contreras, J. and Nogales Espert, A. (2003). *Impact of highly active antiretroviral therapy on the morbidity and mortality in Spanish human immunodeficiency virus-infected children*. Pediatric Infectious Diseases Journal 22(10): 863-7.

Saracino, A., El-Hamad, I., Prato, R., Cibelli, D. C., Tartaglia, A., Palumbo, E., Pezzoli, M. C., Angarano, G. and Scotto, G. (2005). *Access to HAART in HIV-infected immigrants: a retrospective multicenter Italian study*. AIDS Patient Care & STDS 19(9): 599-606.

Saunders, D. S. and Burgoyne, R. W. (2002). *Evaluating health-related wellbeing outcomes among outpatient adults with human immunodeficiency virus*

infection in the HAART era. International Journal of STDs & AIDS 13(10): 683-90.

Sawanpanyalert, P., Yanai, H., Kitsuwannakul, S. and Nelson, K. E. (1996). *An estimate of the number of human immunodeficiency virus (HIV)-positive blood donations by HIV-seronegative donors in a northern Thailand HIV epicenter*. Journal of Infect Disease 174(4): 870-3.

Schechter, M. T., Hogg, R. S., Aylward, B., Craib, K. J., Le, T. N. and Montaner, J. S. (1994). *Higher socioeconomic status is associated with slower progression of HIV infection independent of access to health care*. Journal of Clinical Epidemiology 47(1): 59-67.

Schrooten, W., Dreezen, C., Borleffs, J., Dijkgraaf, M., Borchert, M., De Graeve, D., Hemmer, R., Fleerackers, Y. and Colebunders, R. (2002). *Financial situation of people living with HIV in Europe*. International Journal of STDs & AIDS 13(10): 698-701.

Sendi, P., Gafni, A. and Birch, S. (2002). *Opportunity costs and uncertainty in the economic evaluation of health care interventions*. Health Economics 11(1): 23-31.

Sendi, P. P., Craig, B. A., Pfluger, D., Gafni, A. and Bucher, H. C. (1999). *Systematic validation of disease models for pharmacoeconomic evaluations. Swiss HIV Cohort Study*. Journal of Evaluation in Clinical Practice 5(3): 283-95.

Shaffer, N., Chuachoowong, R., Mock, P. A., Bhadrakom, C., Siriwasin, W., Young, N. L., Chotpitayasunondh, T., Chearskul, S., Roongpisuthipong, A., Chinayon, P., Karon, J., Mastro, T. D. and Simonds, R. J. (1999). *Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a*

randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet 353(9155): 773-80.

Shapiro, M. F., Morton, S. C., McCaffrey, D. F., Senterfitt, J. W., Fleishman, J. A., Perlman, J. F., Athey, L. A., Keesey, J. W., Goldman, D. P., Berry, S. H. and Bozzette, S. A. (1999). *Variations in the care of HIV-infected adults in the United States: results from the HIV Cost and Services Utilization Study*. Journal of the American Medical Association 281(24): 2305-15.

Silversides, A. (2001). *AIDS: after 20 years, complacency*. Canadian Medical Association Journal 165(6): 810.

Sollitto, S., Mehlman, M., Youngner, S. and Lederman, M. M. (2001). *Should physicians withhold highly active antiretroviral therapies from HIV-AIDS patients who are thought to be poorly adherent to treatment?* AIDS 15(2): 153-9.

Souville, M., Msellati, P., Carrieri, M. P., Brou, H., Tape, G., Dakoury, G. and Vidal, L. (2003). *Physicians' knowledge and attitudes toward HIV care in the context of the UNAIDS/Ministry of Health Drug Access Initiative in Cote d'Ivoire*. AIDS 17 Suppl 3: S79-86.

Sperling, R. S., Shapiro, D. E., Coombs, R. W., Todd, J. A., Herman, S. A., McSherry, G. D., O'Sullivan, M. J., Van Dyke, R. B., Jimenez, E., Rouzioux, C., Flynn, P. M. and Sullivan, J. L. (1996). *Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*. New England Journal of Medicine 335(22): 1621-9.

Srasuebkul, P., Ungsedhapand, C., Ruxrungtham, K., Boyd, M. A., Phanuphak, P., Cooper, D. A. and Law, M. G. (2007). *Predictive factors for immunological*

and virological endpoints in Thai patients receiving combination antiretroviral treatment. HIV Medicine 8(1): 46-54.

Stall, R., Pollack, L., Mills, T. C., Martin, J. N., Osmond, D., Paul, J., Binson, D., Coates, T. J. and Catania, J. A. (2001). *Use of antiretroviral therapies among HIV-infected men who have sex with men: a household-based sample of 4 major American cities*. American Journal of Public Health 91(5): 767-73.

Stangl, A. L., Wamai, N., Mermin, J., Awor, A. C. and Bunnell, R. E. (2007). *Trends and predictors of quality of life among HIV-infected adults taking highly active antiretroviral therapy in rural Uganda*. AIDS Care 19(5): 626-36.

Starace, F., Ammassari, A., Trotta, M. P., Murri, R., De Longis, P., Izzo, C., Scalzini, A., d'Arminio Monforte, A., Wu, A. W. and Antinori, A. (2002). *Depression is a risk factor for suboptimal adherence to highly active antiretroviral therapy*. Journal of Acquired Immune Deficiency Syndrome 31 Suppl 3: S136-9.

Steel, J. L., Landsittel, D., Calhoun, B., Wieand, S. and Kingsley, L. A. (2006). *Effects of lipodystrophy on quality of life and depression in HIV-infected men on HAART*. AIDS Patient Care STDS 20(8): 565-75.

Steinbrook, R. (2001). *Providing antiretroviral therapy for HIV infection*. New England Journal of Medicine 344(11): 844-6.

Steinbrook, R. (2002). *Beyond Barcelona--the global response to HIV*. New England Journal of Medicine 347(8): 553-4.

Sterling, T. R., Chaisson, R. E., Keruly, J. and Moore, R. D. (2003). *Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable*

virologic suppression: longer follow-up of an observational cohort study. Journal of Infectious Diseases 188(11): 1659-65.

Stone, V. E., Mansourati, F. F., Poses, R. M. and Mayer, K. H. (2001). *Relation of physician specialty and HIV/AIDS experience to choice of guideline-recommended antiretroviral therapy.* Journal of General Internal Medicine 16(6): 360-8.

Stover, J., Walker, N., Garnett, G. P., Salomon, J. A., Stanecki, K. A., Ghys, P. D., Grassly, N. C., Anderson, R. M. and Schwartlander, B. (2002). *Can we reverse the HIV/AIDS pandemic with an expanded response?* Lancet 360(9326): 73-7.

Strathdee, S. A., Palepu, A., Cornelisse, P. G., Yip, B., O'Shaughnessy, M. V., Montaner, J. S., Schechter, M. T. and Hogg, R. S. (1998). *Barriers to use of free antiretroviral therapy in injection drug users.* Journal of the American Medical Association 280(6): 547-9.

Study, M. (2000). *Costs decline with HAART.* AIDS Patient Care and STDS 14(12): 672.

Svenkerud, P. J. and Singhal, A. (1998). *Enhancing the effectiveness of HIV/AIDS prevention programs targeted to unique population groups in Thailand: lessons learned from applying concepts of diffusion of innovation and social marketing.* Journal of Health Communications 3(3): 193-216.

Taha, T. E., Graham, S. M., Kumwenda, N. I., Broadhead, R. L., Hoover, D. R., Markakis, D., van Der Hoeven, L., Liomba, G. N., Chiphangwi, J. D. and Miotti, P. G. (2000). *Morbidity among human immunodeficiency virus-1-infected and uninfected African children.* Pediatrics 106(6): E77.

Tassiopoulos, K., Williams, P. L., Seage, G. R., 3rd, Crain, M., Oleske, J. and Farley, J. (2008). *Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children*. Journal of Acquired Immune Deficiency Syndrome 47(5): 607-14.

Tershakovec, A. M., Frank, I. and Rader, D. (2004). *HIV-related lipodystrophy and related factors*. Atherosclerosis 174(1): 1-10.

Thailand, N. o. (2005). Chiang Mai Statistics, National Statistical Office of Thailand.

Thaineua, V., Sirinirund, P., Tanbanjong, A., Lallemant, M., Soucat, A. and Lamboray, J. L. (1998). *From research to practice: use of short course zidovudine to prevent mother-to-child HIV transmission in the context of routine health care in Northern Thailand*. Southest Asian Journal of Tropical Medicine and Public Health 29(3): 429-42.

Thanprasersuk, S., Lertpiriyasuwat, C., Tantisak, B., Wongtongkam, N. and Kittimunkong, S. (2004). Situational analysis of the process for developing antiretroviral treatment policy by the royal Thai government. Nonthaburi, Bureau of AIDS, TB and STIs, Department of Disease Control, Ministry of Public Health.

Thanprasertsuk, S., Lertpiriyasuwat, C., Leusaree, T., Sirinirund, P., Sumanapan, S., Chariyalertsak, C., Simmons, N., Ellerbrock, T. V., Siraprapasiri, T., Yachompoo, C., Panputtanakul, S., Virapat, P., Supakalin, P., Srithaniviboonchai, K., Mock, P., Supawitkul, S., Tappero, J. W. and Levine, W. C. (2006). *HIV/AIDS care and treatment in three provinces in northern*

Thailand before the national scale-up of highly-active antiretroviral therapy. Southest Asian Journal of Tropical Medicine and Public Health 37(1): 83-9.

Tourret, J., Tostivint, I., Tezenas Du Montcel, S., Karie, S., Launay-Vacher, V., Vigneau, C., Bessette, C., Deray, G. and Bagnis, C. I. (2007). *Antiretroviral drug dosing errors in HIV-infected patients undergoing hemodialysis*. Clin Infectious Disease 45(6): 779-84.

Trueman, P., Youle, M., Sabin, C. A., Miners, A. H. and Beck, E. J. (2000). *The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom*. HIV Clinical Trials 1(1): 27-35.

UNAIDS (2001). The impact of HIV/AIDS on the health sector in sub-Saharan Africa: The issue of human resources: 64.

UNAIDS (2004). Report on the global AIDS epidemic: Executive Summary. UNAIDS. Geneva, Switzerland.

UNAIDS (2006). *AIDS epidemic update: Special report on HIV/AIDS*.

UNAIDS (2008). Report on the global AIDS epidemic: Joint United Nations Programme on HIV/AIDS (UNAIDS). Geneva.

UNGASS (2008). UNGASS country progress report: Thailand

USAID (2003). The Health Sector Human Resource Crisis in Africa: An Issue Paper, USAID.

Valian, R., Moyle, G. and Reddy, D. (1994). *Physician decision-making in antiretroviral use*. British Journal of Clinical Practice 48(5): 243-5.

van Asten, L. C., Boufassa, F., Schiffer, V., Brettle, R. P., Robertson, J. R., Hernandez Aguado, I., McMenamin, J., Zangerle, R., Fontanet, A., Coutinho, R. A. and Prins, M. (2003). *Limited effect of highly active*

antiretroviral therapy among HIV-positive injecting drug users on the population level. European Journal of Public Health 13(4): 347-9.

van Kooten Niekerk, N. K., Knies, M. M., Howard, J., Rabie, H., Zeier, M., van Rensburg, A., Frans, N., Schaaf, H. S., Fatti, G., Little, F. and Cotton, M. F. (2006). *The first 5 years of the family clinic for HIV at Tygerberg Hospital: family demographics, survival of children and early impact of antiretroviral therapy*. Journal of Tropical Pediatrics 52(1): 3-11.

van Sighem, A., Danner, S., Ghani, A. C., Gras, L., Anderson, R. M. and de Wolf, F. (2005). *Mortality in patients with successful initial response to highly active antiretroviral therapy is still higher than in non-HIV-infected individuals*. Journal of Acquired Immune Deficiency Syndrome 40(2): 212-8.

Volberding, P. S. and Graham, N. M. (1994). *Initiation of antiretroviral therapy in HIV infection: a review of interstudy consistencies*. Journal of Acquired Immune Deficiency Syndrome 7 Suppl 2: S12-22; discussion S22-3.

Walsh, B., Steiner, A., Pickering, R. M. and Ward-Basu, J. (2005). *Economic evaluation of nurse led intermediate care versus standard care for post-acute medical patients: cost minimisation analysis of data from a randomised controlled trial*. British Medical Journal 330(7493): 699.

Walsh, J. C., Horne, R., Dalton, M., Burgess, A. P. and Gazzard, B. G. (2001). *Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes*. AIDS Care 13(6): 709-20.

Ware, N. C., Wyatt, M. A. and Tugenberg, T. (2006). *Social relationships, stigma and adherence to antiretroviral therapy for HIV/AIDS*. AIDS Care 18(8): 904-10.

Waters, L., Stebbing, J., Jones, R., Michailidis, C., Sawleshwarkar, S., Mandalia, S., Bower, M., Nelson, M. and Gazzard, B. (2004). *A comparison of the CD4 response to antiretroviral regimens in patients commencing therapy with low CD4 counts*. Journal of Antimicrobial Chemotherapy 54(2): 503-7.

Weiss, L., French, T., Finkelstein, R., Waters, M., Mukherjee, R. and Agins, B. (2003). *HIV-related knowledge and adherence to HAART*. AIDS Care 15(5): 673-9.

WHO (2002). *3 million HIV/AIDS sufferers could receive anti-retroviral therapy by 2005*. Indian Journal of Medical Sciences 56(9): 456-7.

WHO (2002). *Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach. Executive summary. April 2002*. IAPAC Monthly 8(6): 168-75.

WHO. (2004). *The monitoring and evaluation (M&E) of the 3 by 5 initiative*. Retrieved March 8th, 2005, from http://www.who.int/3by5/publications/briefs/en/m&e.pdf.

WHO. (2004). *Working Document on Monitoring and Evaluating of National ART Programmes in the Rapid Scale-up to 3 by 5*. Retrieved March 8th, 2005, from http://www.who.int/3by5/publications/documents/en/3by5_monitoring_evaluation.pdf.

WHO and UNAIDS *3 by 5 Progress Report: December 2003 through June 2004*, WHO and UNAIDS.

Wolf, M. S., Davis, T. C., Arozullah, A., Penn, R., Arnold, C., Sugar, M. and Bennett, C. L. (2005). *Relation between literacy and HIV treatment knowledge among patients on HAART regimens*. AIDS Care 17(7): 863-73.

Wolf, M. S., Davis, T. C., Osborn, C. Y., Skripkauskas, S., Bennett, C. L. and Makoul, G. (2007). *Literacy, self-efficacy, and HIV medication adherence.* Patient Education & Counselling 65(2): 253-60.

Wood, E., Hogg, R. S., Yip, B., Dong, W. W., Wynhoven, B., Mo, T., Brumme, C. J., Montaner, J. S. and Harrigan, P. R. (2005). *Rates of antiretroviral resistance among HIV-infected patients with and without a history of injection drug use.* AIDS 19(11): 1189-95.

Wood, E., Hogg, R. S., Yip, B., Harrigan, P. R. and Montaner, J. S. (2004). *Using baseline CD4 cell count and plasma HIV RNA to guide the initiation of highly active antiretroviral therapy.* Revista de Investigatione Clinica 56(2): 232-6.

Wood, E., Montaner, J. S., Bangsberg, D. R., Tyndall, M. W., Strathdee, S. A., O'Shaughnessy, M. V. and Hogg, R. S. (2003). *Expanding access to HIV antiretroviral therapy among marginalized populations in the developed world.* AIDS 17(17): 2419-27.

Wood, E., Montaner, J. S., Chan, K., Tyndall, M. W., Schechter, M. T., Bangsberg, D., O'Shaughnessy, M. V. and Hogg, R. S. (2002). *Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996.* AIDS 16(15): 2065-72.

Wood, E., Montaner, J. S., Chan, K., Tyndall, M. W., Schechter, M. T., Bangsberg, D., O'Shaughnessy, M. V. and Hogg, R. S. (2002). *Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996.* AIDS 16(15): 2065-72.

Wu, A. W. (2000). *Quality of life assessment comes of age in the era of highly active antiretroviral therapy.* AIDS 14(10): 1449-51.

Wu, A. W., Jacobson, K. L., Frick, K. D., Clark, R., Revicki, D. A., Freedberg, K. A., Scott-Lennox, J. and Feinberg, J. (2002). *Validity and responsiveness of the euroqol as a measure of health-related quality of life in people enrolled in an AIDS clinical trial*. Quality of Life Research 11(3): 273-82.

Wu, A. W., Mathews, W. C., Brysk, L. T., Atkinson, J. H., Grant, I., Abramson, I., Kennedy, C. J., McCutchan, J. A., Spector, S. A. and Richman, D. D. (1990). *Quality of life in a placebo-controlled trial of zidovudine in patients with AIDS and AIDS-related complex*. Journal of Acquired Immune Deficiency Syndrome 3(7): 683-90.

Wu, A. W., Rubin, H. R., Mathews, W. C., Brysk, L. M., Bozzette, S. A., Hardy, W. D., Atkinson, J. H., Grant, I., Spector, S. A., McCutchan, J. A. and et al. (1993). *Functional status and well-being in a placebo-controlled trial of zidovudine in early symptomatic HIV infection*. Journal of Acquired Immune Deficiency Syndrome 6(5): 452-8.

Yamey, G. (2000). *Drug companies cut HIV drug prices in the developing world.* British Medical Journal 320(7246): 1357.

Yarchoan, R., Venzon, D. J., Pluda, J. M., Lietzau, J., Wyvill, K. M., Tsiatis, A. A., Steinberg, S. M. and Broder, S. (1991). *CD4 count and the risk for death in patients infected with HIV receiving antiretroviral therapy*. Annals of Internal Medicine 115(3): 184-9.

Yazdanpanah, Y. (2004). *Costs associated with combination antiretroviral therapy in HIV-infected patients*. Journal of Antimicrobial Chemotherapy 53(4): 558-61.

Yen, C. F., Tsai, J. J., Lu, P. L., Chen, Y. H., Chen, T. C., Chen, P. P. and Chen, T. P. (2004). *Quality of life and its correlates in HIV/AIDS male outpatients*

receiving highly active antiretroviral therapy in Taiwan. Psychiatry Clinical Neuroscience 58(5): 501-6.

Zaccarelli, M., Barracchini, A., De Longis, P., Perno, C. F., Soldani, F., Liuzzi, G., Serraino, D., Ippolito, G. and Antinori, A. (2002). *Factors related to virologic failure among HIV-positive injecting drug users treated with combination antiretroviral therapy including two nucleoside reverse transcriptase inhibitors and nevirapine*. AIDS Patient Care and STDS 16(2): 67-73.

Zhang, Z., Hamatake, R. and Hong, Z. (2004). *Clinical utility of current NNRTIs and perspectives of new agents in this class under development*. Antiviral Chemistry & Chemotherapy 15(3): 121-34.